THE METABOLIC BRAIN DISEASES AND THEIR TREATMENT

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IN MILITARY AND CIVILIAN PRACTICE

By

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PREFACE

It is the hope of the author that this work will provide material for discussion and profitable controversy among psychiatrists, in addition to arousing the interest of those medical men who are engaged in other branches of medicine than psychiatry, in a subject which has come greatly into prominence within recent years.

It is probable that no medical discovery has been the subject of so much dispute and so many theories and hypotheses as has the neurometabolic or, to give it its popular name, "shock" treatment of the major mental disorders. In nearly every publication which has appeared on the subject, will be found the oft-repeated statement that it is a purely empirical form of treatment and that the mode of action is unknown; and, in spite of the enormous amount of literature and research which has been published, no-one has yet ventured to give a satisfactory answer to the two important questions: What is the pathophysiological basis, if any, of the conditions known generally as the schizophrenic, delusional, and affective psychoses? and, What is the physiological and chemical mechanism of the insulin and "shock" therapies?

The author hopes that this work will provide a possible answer to both these questions, in addition to a classification and terminology for these diseases which, in contrast to those hitherto in general use, offers the advantages of accuracy, simplicity, and a minimum of long Greek words.

In the ensuing pages the controversy now raging of physical versus psychotherapeutic methods of treatment is fully discussed, as also are certain fallacies which have grown up recently around the subject of neurometabolic therapy and the clinical symptomatology of the metabolic brain-diseases. In the chapters on cerebral biochemistry and the biological changes in neurometabolic therapy, extensive use has been made of the brilliant work of Himwich, Gellhorn, and others of the American school of psychophysiology, to whose researches insufficient attention has been paid in this country.

The limitations and pitfalls of neurometabolic therapy are also fully discussed in these pages, and the author hopes that the reader will be able to form a balanced view of the subject, midway between the elation and optimism with which the new forms of treatment were greeted at their inception, and the reactionary swing towards scepticism and therapeutic nihilism which has resulted within the last few years.

G. T. S.

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NOTE ON THE TERMINOLOGY EMPLOYED

ENCEPHALOPATHY, ENCEPHALOPATHIC. *Used throughout the book in place of "Psychosis" and "Psychotic," these last two terms being dropped altogether for descriptive purposes.*

METABOLIC ENCEPHALOPATHY. *General term used to embrace all the conditions commonly termed "Psychogenic Psychoses" or "Constitutional Psychoses" in orthodox terminology—e.g., schizophrenia, affective, and delusional conditions. Certain drug encephalopathies are also included as well as some types of traumatic and toxi-infective states. It does not include the "organic reaction types," such as paresis, senile, and arteriosclerotic insanities, for which the term "ORGANIC ENCEPHALOPATHY" is employed.*

DYSOXIC ENCEPHALOPATHY, or DYSOXIA. *One of the two main clinical sub-divisions of metabolic encephalopathy. It includes the affective states and certain forms of paranoid, katatonic, and mixed depressive schizophrenic conditions. Some forms of obsessional states and conditions characterized by depersonalization are also included.*

DYSGLYCIC ENCEPHALOPATHY or DYSGLYCIA. *The other main subdivision of metabolic brain-disease. It includes the conditions of hebephrenia, schizophrenia, paraphrenia, and paranoia.*

NEUROMETABOLIC THERAPY. *Term used throughout in place of "Shock Therapy," a name which has acquired some unfortunate connotations, and is for this reason dropped entirely.*

ANOXIC THERAPY. *Used in place of "Convulsive Therapy" for the same reason. Includes all methods of inducing anoxic convulsions, whether physical or pharmacological.*

ELECTROANOXIA. *Used throughout in place of "Electroconvulsive Therapy," or "Electrical Shock-Therapy."*

HYPOGLYCÆMIA. *Used as synonymous with "Insulin Therapy" and "Insulin-Shock."*

SENSORY. *Used as equivalent term for "Paranoid" or "delusional."*

THE METABOLIC BRAIN DISEASES AND THEIR TREATMENT

CHAPTER I

INTRODUCTORY

Scientific progress, particularly in medicine, advances not by a steady and continual process, but in a series of leaps and bounds, separated by intervals of apparent stagnation. Thus, in general medicine during the last seventy years we have seen a series of prolonged periods of inertia, punctuated by such brilliant advances as, for instance, the discovery of bacteria, insulin, the sulphonamides, and finally, penicillin, in chronological order.

The same has been the case with psychiatry, a branch of medicine which hardly existed seventy years ago. As late as the middle of the last century, the treatment of the major mental disorders in many countries remained crude and unscientific, while the psychoneuroses were hardly recognized as diseases at all. It was not until the work of Freud, Bleuler, Kraepelin, and other leading psychopathologists at the end of the last century that the science of signs and symptoms as applied to psychiatry was first put on a sound basis. These workers concentrated mainly on the psychopathological aspects of mental disorder, and it was not until the twenties of the present century that the first great advance in the physical therapy of a major mental disorder was successfully made. This was the introduction of the induced malarial therapy of general paresis by Wagner-Jauregg.

Following this advance, there was another period of stagnation of over fifteen years; then, in the middle thirties, occurred the next great advance, the discovery of the hypoglycæmic method of therapy by Sakel, and the convulsive or anoxic therapy by Meduna, for the conditions henceforth referred to in this work as the metabolic brain-diseases, or metabolic encephalopathies. The first outstanding step had been made in the treatment of these conditions, whose therapy had up to that time been as discouraging as their cause had been mysterious.

The anoxic form of therapy had, however, one very serious drawback; it was extremely frightening and disagreeable for the patient, as all those who have used the cardiazol and triazol

technique of induction will agree. This disadvantage was completely eliminated by the next advance, namely the brilliant work of Cerletti and Bini on the electrical method of introducing therapeutic convulsions, which has now entirely replaced the use of convulsant drugs.

The introduction of neurometabolic therapy has within the last ten years opened up not only a new era, but a completely new branch of psychiatry, that of biochemical therapy. Not only do we now possess a specific therapy for conditions of brain-disease which up to a few years ago nearly always had a hopeless prognosis, but these methods have opened up a completely new conception of the pathology and causation of these disorders, whose true nature had previously been an insoluble mystery.

Nevertheless, even after the introduction of the neurometabolic form of therapy, the psychiatrist still laboured under a great disadvantage in his work as compared with the surgeon and the general physician for two reasons.

First, the work of the latter is always based on a known organic pathology and morbid anatomy of the conditions which he is called upon to treat ; the psychiatrist, on the other hand, has up to now had no organic pathology on which to base his deductions and therapeutic procedures. As an earlier writer well expressed it, " Pathology is silent as to the seat of madness " ; and in consequence, the work of the psychiatrist was based almost entirely on psychopathological concepts of the psychoanalytic and kindred schools of thought. These, although they explained to a large extent the mental mechanisms and conflicts which determine the mode of precipitation and symptomatology of the conditions under consideration, threw little or no light upon the actual morbid process in the brain-tissues underlying them.

Second, the difficulties of the psychiatrist in his conception of mental disorders and their description have been greatly increased by the lack of a satisfactory terminology and ætiological classification. The various classifications which have been proposed up to the present time are all based on symptomatology and not on the morbid anatomy of the conditions described, in contrast to what is found in general medicine and surgery.

Moreover, during the period immediately preceding the discovery of neurometabolic therapy, psychiatric therapy was to a very large extent dominated by the teachings of the psychoanalytic and allied schools, which laid emphasis on purely psychogenic rather than physical mechanisms as the underlying

causes of mental disorder. The result of this was that treatment was looked upon in all cases as primarily psychotherapeutic, the physical aspects being regarded as relatively unimportant. The possibility that symptoms which were purely mental might be due to a purely physical process did indeed occur to some workers, and when orthodox psychotherapeutic methods had signally failed when confronted with the encephalopathic group of disorders, an assiduous search was commenced for a possible physical factor in their causation. Septic foci, hormones, infections, and vitamin-deficiency were in turn inculpated and strenuously dealt with, all to no result, so that the psychogenic theory of causation of the encephalopathies once more held the field. It needed the purely fortuitous discovery of the remarkable effects of hypoglycæmia and induced convulsions—accidental, as so many major medical discoveries have been—to revive once more the hypothesis of a physical causation, and to point the way to a true understanding of their genesis and pathology. This is a remarkable example of how a purely accidental discovery and empirical therapy can lead up to an entirely new conception of the method of approach to a problem of this kind.

In this way, despite the undeniably great achievements of the psychogenic schools of thought, they undoubtedly did a disservice to psychiatry, and to this day the physiogenic school of opinion is but slowly gaining ground in the face of fixed and tradition-hallowed ideas. Those who hold to the view of a physical causation are to this day in a minority compared with the large number of eminent authorities who still adhere to the theory of primarily psychogenic causation of the metabolic group of mental disorders.

In view of these facts, it is not surprising that the anoxic and hypoglycæmic therapies have up to now been entirely empirical; various theories of their mode of action have been advanced, none of which have adequately and satisfactorily explained the pathological basis of the conditions variously known by such terms as schizophrenia and the affective and delusional psychoses. Furthermore the position has not been improved by the fact that prejudice and preconceived ideas die hard. Indeed, quite recently, powerful efforts have been made by some of the more conservative and misoneistic schools of thought to discredit the efficacy and possibilities of the new therapy, and to allege that it involves risks and complications of a fearsome kind, which discount entirely its possible advantages and benefits

This is, of course, to a large extent a natural reaction from the unfortunate publicity and over-optimistic enthusiasm with which the new treatment was hailed at its inception both in the medical and popular press. Indeed, soon after its introduction into this country, neurometabolic therapy was applied indiscriminately by its enthusiasts to a variety of mental disorders of all kinds, from low-grade mental deficiency to anxiety-hysteria ; so that the resulting large percentage of therapeutic failures tended to produce a reaction of scepticism and therapeutic nihilism. This is an excellent example of what happens when a new treatment is applied without discrimination or proper knowledge of the nature and pathology of the conditions treated, and the importance of such knowledge before attempting treatment, both in psychiatry as well as in general medicine could not better be illustrated.

As a result, however, of the researches of Golla, Himwich, Quastel and other workers into the chemistry of cerebral metabolism and its anomalies in the major mental disorders, much of the mystery surrounding these conditions and the mode of action of neurometabolic therapy has now been largely dispelled. The hypothesis of a primary metabolic disorder of the cerebral biochemistry—henceforth to be referred to in this work as metabolic encephalopathy—has been gaining ground steadily as the result of these discoveries in the course of the last few years.

The ensuing pages will be devoted to the elaboration of this concept, and the demonstration that it is the only possible and satisfactory working hypothesis which is in accordance with the known facts and can adequately explain the phenomena of these disorders and of the anoxic and hypoglycæmic therapies. This new conception of the pathology of these diseases will be presented, the material being based on studies of several hundred acute and typical cases treated by the writer during the last five years. In addition, a practical suggestion will be presented for a simplified and more accurate classification and terminology than those hitherto in use in the orthodox psychiatric text-books.

The subject-matter presented is based on studies extending over a period of more than five years intensive experience of the use of the new therapies in various military hospitals. Military psychiatry offers unique opportunities in this respect for the following reasons.

Firstly, the turnover of recent and acute cases of the dysglycic and dysoxic syndromes in a military psychiatric unit is much larger than that of the ordinary civilian mental hospital, where of

necessity a large proportion of the clinical material consists of advanced and chronic cases, senile conditions and deteriorated encephalopathics, which represent only the end-stages of a prolonged morbid process, and in which the therapeutic possibilities are for the most part extremely poor.

Secondly, the subjects studied by the author were in nearly all cases healthy males of military age—that is, of the age-group 18 to 35 years, the age-period in which dysoxic and dysglycic encephalopathies are commonest, and most often seen in their acute and typical form.

Thirdly, the peculiar conditions of military service and the provision of an efficiently organized military psychiatric service ensure that early cases of these conditions are detected and referred for treatment in their early stages. In civilian practice, on the other hand, it is often surprising for how long cases of manifest encephalopathic illness are allowed to go on before being brought to the psychiatrist for treatment. Under the conditions of service life, however, it is inevitable that any peculiarity of behaviour or change in a soldier's personality as shown by loss of efficiency or behaviour-disorder is quickly detected by his superiors, and the man referred for psychiatric opinion and treatment before deterioration and irreversible neuronal changes have supervened. Indeed, a very large proportion of cases are detected and admitted for treatment during the first few weeks or even days of their disorder.

It will be evident from these considerations that military psychiatry presents one great possibility for the study of these conditions which is denied to the civilian psychiatrist. The subjects available are young and physical healthy adults, whose disease is in the early and reversible phase, so that clinical observations and therapeutic results are not vitiated by the presence of secondary deterioration due to chronic mental degeneration and co-existing physical disease, as is so often found in the chronic hospitalized cases seen in civilian mental hospital practice.

The conditions dealt with in this work are those commonly known in the orthodox terminology as the schizophrenic, affective, and delusional psychoses. They form by far the largest proportion of cases admitted to a military psychotic unit, as would naturally be expected from a consideration of the age-groups encountered. The depressions of later life are rarely found, while the dysoxic reaction-type in its various forms is by far the most numerous.

The type of reaction found is in all respects similar in symptomatology, course and prognosis to that encountered in civilian practice. It can here be stated, contrary to a widespread belief that there is no special type of psychosis peculiar to wartime conditions—unless the peculiar hysteroencephalopathic syndrome discussed in a subsequent chapter can be so described. As would naturally be expected, the florid and acute symptoms are often coloured by the patient's war experiences, particularly in cases where the breakdown has occurred under front-line conditions and where battle-experiences form a large part of the delusional and hallucinatory content of the encephalopathy ; but the psychosomatic mechanisms, course, and evolution of the disorder follow the same lines as those of civilian cases.

As would be expected, the acute and typical encephalopathies are much more commonly found than in civil practice ; thus, for example, the acute confusional forms of malignant dysglycia and dysoxia are extremely common, while the chronic delusional states of later life and the true manic-depressive states are comparatively infrequent. The hysteroencephalopathic syndrome appears to be almost peculiar to military conditions in which there is exposure to severe stress. Almost all cases which present a predominantly manic-depressive type of symptomatology eventually prove to be examples of the malignant dysoxic or dysglycic encephalopathy ; the true affective (manic-depressive) form of dysoxia is quite a rarity.

Conditions such as epileptic states, deficiency-diseases, organic encephalopathies, and the neuroses, are outside the scope of this work except in so far as they present problems in the differential diagnosis of the metabolic disorders. Similarly, the writer has not ventured on any detailed discussion of the mental mechanisms and psychopathology of the metabolic encephalopathies, since this subject has already been dealt with at length in the orthodox text-books on psychoanalysis and psychopathology. The ensuing pages deal with the subject from the organic and biochemical point of view, since in the writer's view the conditions under discussion are organic diseases, and their therapy essentially physical and pharmacological. The clinical and experimental evidence in support of this view will be fully discussed in the subsequent chapters.

In the same way, in order to avoid needless repetition, the writer has omitted any detailed description of the actual technique of anoxic and hypoglycæmic therapy. Many concise and excel-

lent monographs dealing with this aspect have already been published, and a list of these for reference purposes is included in the bibliography and appendix at the end of this volume. A later chapter is, however, devoted to a detailed discussion of certain important points in the practical application of neurometabolic therapy, including some notes on the forms of electro-convulsive apparatus in general use at the present day.

One other notable omission will be apparent to the reader who is familiar with the orthodox form of medical treatise. This is the absence of the usual masses of figures, percentages, and statistics without which no text-book or article of this kind is nowadays considered complete. The writer's experience has amply justified the view that human patients and their diseases cannot be reduced to any kind of rule of thumb or figures, and that the only reliable guide to correct deduction and clinical knowledge is actual and accurate observation of the living patient at the bedside. It is indeed remarkable that, since the inception of the neurometabolic therapies, various statisticians have successfully " proved " that, on the one hand, a ninety per cent. recovery rate may be expected in patients treated by biophysical methods when compared with controls, and on the other, that neurometabolic therapy is quite ineffective, and that in any series of cases the controls always show much better results than the treated cases. The futility of the statistical method of assessing therapeutic results therefore needs no further comment. Furthermore, the writer feels that all readers will agree that there is probably no task more tedious and hypnogenic than the perusal of a medical treatise which consists mostly of interminable columns of figures and statistics strung together with a few badly-constructed sentences and paragraphs of indifferent English. Medicine, unlike physics or astronomy, is not an exact science, and the human body and personality abides by no fixed and rigid laws of mathematics.

The ensuring subject-matter will be devoted to a brief description of the normal cerebral biochemical mechanisms, with particular reference to recently discovered facts regarding cerebral respiration and oxygen-glucose metabolism, followed by a description and discussion of the two main types of metabolic disorder and their genesis. The hypothesis of a disturbance of cerebral oxygen-glucose metabolism as the basis of the major mental disorders will then be reviewed, and the new classification of these conditions proposed by the writer will be presented and described in detail.

CHAPTER II

NORMAL CEREBRAL METABOLISM AND ITS DISORDERS.

(1) Biochemistry of the Normal Brain.

It is now generally agreed that the two essential chemical substances required for normal function in cerebral tissue are oxygen and glucose. The latter is, in fact, probably the only kind of fuel utilized by the brain-tissue to provide the energy required for its activities. Two principal reactions are involved in glucose-metabolism—oxidation, and glycolysis, both aerobic and anaerobic, and it appears probable that these processes are carried out by two main types of neurons, the oxidizing cells and glycolysing cells respectively, the two reactions being, as would naturally be expected, interdependent to a large extent.

The glucose supplied to the brain by the blood-stream may be utilized in three different ways ; it may be stored as glycogen, as in the liver and other organs, glycolysed and eliminated as lactate by the glycolysing cells, or oxidized completely to lactate by the oxidizing cells.

The most important fact recently discovered regarding glycolysis is that it is effected by means of a phosphorylation-mechanism, similar to that of muscular tissue. Experimentally, it is found that, when cell-free extracts of normal brain-tissue are incubated in the presence of fluoride with glucose and inorganic phosphate, the latter disappear giving rise to phosphorylated products, which include fructose diphosphate, phosphoglyceric acid, and glucose-hexophosphate, the last-named being possibly the primary product. The essential components for this reaction are an oxidizable substrate, such as citrate, glutamate, or succinate, adenylic acid, cozymase, and magnesium ions. The adenylic acid acts as a phosphate-carrier, the oxidizable substrate being required to provide the necessary energy for the reaction. Pyruvic acid can serve in this way as substrate in the presence of fumaric acid.

For glycogen-synthesis, as in other organs, glycose mono-phosphate is required by the brain ; this is obtained through the reversible catalyzation of the interconversion of glucose mono- and hexo-phosphates by the enzyme phosphoglucomutase. For the actual process of glycolysis, the brain requires inorganic phosphate, adenosine triphosphate, cozymase, and magnesium ions.

In glucose-oxidation, the main path of carbohydrate-breakdown is through the oxidation of pyruvic acid, as glucose cannot be directly oxidized to lactic acid and carbon dioxide. In the glycolysing cells, the pyruvate competes with oxygen as hydrogen acceptor, and is reduced to lactate, while in the non-glycolysing cells it is oxidized to carbon dioxide. It is quite possible that it is these two mechanisms which are at fault in the dysoxic and dysglycic states described in a subsequent chapter.

Pyruvic acid is decarboxylated to acetaldehyde and carbon dioxide by an enzyme which is present in brain and other tissues, the carbon dioxide being produced both aerobically and anaerobically. For this reaction, magnesium ions and phosphorylated vitamin Bi are necessary. Pyruvic acid may react in as many as sixteen different ways, according to the concentration, permeability-factors, PH, presence of vitamin Bi, and so on. The last-named substance is concerned in the oxidation of pyruvate in all tissues.

The intermediate oxidation-mechanisms are principally effected through the cytochrome-oxidase system. The dehydrogenases catalyse the transfer of hydrogen from the oxidizable metabolites of the cells to the cytochromes, and the cytochrome-oxidase then catalyses the oxidation of cytochromes by molecular oxygen.

Our knowledge of the actual respiration-mechanisms of normal brain-tissue is largely due to the researches of Quastel and his colleagues in this country, and of Himwich in America. Two methods of investigation are available for studies of this kind; direct observation of the chemical changes which take place when isolated portions of cerebral tissue are incubated in vitro, either with different concentrations of drugs or the natural metabolites; and indirect observation in the intact animal or human subject, by taking and estimating samples of blood from the internal carotid artery and internal jugular vein. This can be done both in the resting state and when the subject is under the influence of drugs, electroanoxia, or inhalation of gases. In the case of *in vitro* studies, animal brains, minced or in slices, are usually employed.

It will be evident that in the study of cerebral metabolism indirect methods of observation have to be relied upon, since there is no method known at present by which we can make direct observation of the processes going on inside a nerve-cell while it is *in situ* in the living organism. The disadvantage of the *in vitro*

method is that the results observed are applicable only to isolated neurons under conditions totally different from those obtaining in the intact body. The arterio-venous technique, however, has the advantage of being applicable to the human subject, although it is at best an indirect method of observation. In spite of these disadvantages, however, much useful knowledge of the oxidation-mechanisms of cerebral tissue has been gained as the result of experiments of this kind.

These investigations abundantly confirm the view that carbohydrate in the form of glucose is the essential fuel of the brain, for the following reasons. The respiratory quotient of cerebral tissue has been found to be unity, and estimations of the sugar-content of the blood in the internal carotid and internal jugular vein show that carbohydrate is lost during the passage of the blood through the cerebral circulation. The approximate value of the amount of glucose consumed under resting conditions by the brain *in vivo* is 10 milligrams per 100 ccs. of blood, and the amount of oxygen required to burn this weight of glucose completely is 7.5 ccs. This figure is found to correspond closely to the actual fall in oxygen-content of the blood passing through the cerebral circulation.

Again, in experiments on the oxygen-consumption of the brain in the amytalized dog, it is found that the amount of glucose consumed is 13 milligrams per 100 ccs. This corresponds to an oxygen-consumption of 9.7 ccs. per 100 ccs. of blood; the average difference in oxygen-content between arterial and venous blood is very nearly the same, the actual figure being 9.3 ccs. per 100 ccs. of blood. The average oxygen-consumption in the intact brain has been found to be of the order of 8 ccs. per 100 ccs.

The oxygen-content of the blood on leaving the brain is found to equal 60 per cent. of the normal saturation-value, and less than that leaving the face and limbs. Of all parts of the brain, the grey matter has been found to have the highest rate of oxygen-consumption, which would naturally be expected, since it contains the highest concentration of actively respiring nerve-cells.

Cerebral oxygen-glucose metabolism is inhibited by narcotics, which prevent the uptake of oxygen by the brain-cells. A similar effect is found with toxic amines, such as indole, B-phenylethylamine, and mescaline, which depress the oxidation of glucose and sodium lactate, but not that of succinate. The action of amines is reversible, except in the case of mescaline, in which it is complete; this last-mentioned substance and its peculiar

cerebral action will be further discussed in a later section of this chapter. Normally, toxic amines are oxidized by the enzyme amine-oxidase to ammonia ; in the case of mescaline, however, this does not occur.

The cyanides also have a powerful inhibitory effect on cerebral respiration ; it has been found that they act by inhibition of the cytochrome-oxidase group of enzymes. This is proof that cytochrome-oxidase activity is quantitatively the most important mechanism for oxygen-activation.

The electrical potentials of the brain, as seen in the electro-encephalogram, are abolished by anoxæmia or narcotic poisoning.

Cerebral respiration is stimulated by substances such as benzedrine, p-phenylenediamine, thyroid, and the analeptics (coramine, cardiazol, and triazol).

Mention has already been made of the importance of the pyruvic acid mechanism in the oxidation of glucose. As previously stated, glucose cannot be directly oxidized to carbon dioxide and water, but requires the intermediate stage of pyruvic acid. In animal experiments it is found that pyruvate is highly effective in maintaining the cerebral respiration when added to living brain-tissue *in vitro*, since it is rapidly oxidized and disappears in such preparations. Nevertheless, neither pyruvate, lactate, or succinate can replace glucose completely as the cerebral fuel, since in hypoglycæmic therapy it is found that none of these substances are effective in counteracting the hypoglycæmia and rousing the comatose patient. This is another striking piece of evidence that glucose is the essential and only fuel utilized in the normal cerebral respiratory process.

Abnormalities of glucose-oxygen and pyruvic acid metabolism are found in certain forms of congenital mental abnormality, such as mongolism, epileptic states, and phenylpyruvic oligophrenia.

(2) Disorders of Cerebral Metabolism.

Reference has already been made to the practical difficulties encountered in making observations of human brain-metabolism, and in attempting to apply the results of experiments on isolated brain-tissue *in vitro* to the living subject. Nevertheless, a number of striking facts are known in clinical medicine which provide strong evidence in support of the hypothesis that, in the absence of any detectable pathological lesion of the brain, mental disturbances of a gross nature can be produced purely as the result of interference with the normal cerebral respiratory processes.

Thus, it is well-known that, in the metabolic encephalopathies, no organic pathology is found in the early stages, and the same holds good for the group of disorders generally known as the psychoneuroses. There is, however, a fundamental difference between the two varieties of mental conditions; neurotic symptoms can be induced experimentally both in animals and in human subjects by means of purely psychological methods, as was demonstrated in the famous experiments of Pavlov on conditioned reflexes in the dog. The symptoms of metabolic encephalopathy, however, cannot be reproduced experimentally in the normal individual by such methods, but only by interfering with the cerebral respiratory process, by means of either physical or pharmacological agents.

Increasing stress has been laid in recent years on the importance of anoxæmia and the extreme sensitivity of the brain-tissues thereto in the genesis of mental disorders. Thus, the immediate and dramatic disturbance of consciousness which accompanies compression of the carotids and consequent acute cerebral anoxæmia is well-known. Again, encephalopathic symptoms can readily be produced in the normal subject by the inhalation of such agents as nitrous oxide, ether, and other anæsthetics, all of which are known to act by producing cerebral anoxia and so by depression of the cerebral respiration-mechanisms. The symptoms so produced include vivid hallucinations, mental confusion, disturbances of spatial and temporal perception, affective phenomena such as elation and exhilaration, and motor symptoms in the form of excitement and maniacal behaviour. Another well-known example of psychical effects of cerebral anoxæmia is the phenomena of mountain-sickness in climbers and of high-altitude flying in aviators, where insufficient precautions are taken to ensure a proper oxygen-supply. A characteristic train of symptoms is seen in these conditions, which includes disorders of memory, temporal and spatial perception, defective judgment and discrimination, loss of normal emotional inhibition with elation and euphoria of pathological type, and impairment of visual discrimination. Experimental overbreathing, or that found in certain hysterical states, may produce similar effects Also, chronic conditions of obstruction of the upper respiratory passages very often set up secondary mental disturbances, by reason of the state of subacute cerebral anoxæmia which they produce; such symptoms include feelings of fatigue, mild depression, hebetude and difficulty in concentration of varying degree,

Another classical example of a toxin which acts by virtue of a specific depressant effect on the oxidation processes is alcohol ; the effects are seen as the ordinary acute syndrome of alcoholic intoxication, and in the form of dysoxic encephalopathy sometimes known by the term of " alcoholic paranoia " or " alcoholic hallucinosis." Alcohol can also produce typical dysglycic symptoms, in the form of delirium tremens.

The action of narcotics, such as the barbiturates, chloral, and bromides in depressing brain-metabolism has already been referred to. In bromide and barbiturate encephalopathy, dysoxic symptoms in the form of hebetude, confusion, and depression generally predominate, but dysglycic states in the form of acute excitement, hallucinosis, and mania are occasionally seen.

Of agents which have a specific action on the glycolysing functions, the best-known is insulin when given in toxic dosage. Its cerebral effects are seen typically in diabetics who have taken an accidental overdose, and in hypoglycæmic therapy. The symptoms are usually of typical dysglycic form, such as elation. overactivity, flight of ideas, maniacal behaviour, and sometimes hallucinosis.

The euphoriant group of drugs, whose action is confined almost entirely to the higher centres, also acts by depressing the cerebral respiratory mechanism, as is shown in experiments on sliced animal brain exposed to them in different concentrations. Thus, the phenanthrene (morphine) and dibenzopyran (cannabis) groups of narcotics have a specific depressant effect on the oxidation-processes ; this seems to be the principal action of the first-named compounds, while the cannabis group also produce typical dysglycic effects in the form of hallucinosis, elation, excitement, and personality-disorders.

It will be evident from a consideration of these facts that toxic agents can produce their effect upon the psychic functions in three possible ways : by inhibiting either oxidation or glycolysis, or by a combination of both reactions.

It will have been noted that all the agents described above, with the possible exception of cannabis, are drugs which produce toxic effects on the vital functions, and that none of them possess the property of reproducing typical encephalopathic symptoms, such as auditory hallucinosis, delusions of persecution, and thought-disorder, unless they are administered in dosage sufficient to cause toxic symptoms. In other words, none of them has the specific effect of modifying the metabolism of the higher psychic

centres, while at the same time leaving that of the lower levels unaffected. The important question now arises; is there any pharmacological agent known which possesses this property?

Mention has already been made in connection with the toxic amines of mescaline and its irreversible action on the cerebral oxidation-process. This drug stands in a class by itself among the euphoriant group of alkaloids, and its remarkable cerebral effects merit a special description for this reason. Since its discovery at the end of the last century, it has been made the subject of a large amount of literature and research, principally with reference to its characteristic effects on visual and temporal perception. In a previous paper, the writer described a series of experiments with the drug on a group of normal subjects of different personality-types, and showed that it reproduces under experimental conditions all the mental phenomena which are found in the dysoxic and dysglycic encephalopathies.

(3) Mescaline Encephalopathy.

Mescaline is an alkaloid of the toxic amine group, and is the active principle of the peyote cactus (*Anhalonium Lewinii*), which grows in the deserts of Northern Mexico, where it is used as a ritual intoxicant by the native tribes. Chemically, it is a well-defined compound, β-3-4-5-trimethoxy-phenylethylamine, and possesses the physical and chemical properties usual to alkaloids. Its mode of action on the brain has already been indicated. Pharmacologically, it resembles cannabis indica most closely in its psychological action, but also resembles the atropine alkaloids in some respects, notably in its very powerful mydriatic effect and inhibitory action on the parasympathetic system. Its principal effect, however, is upon the higher psychic centres, the toxicity being very low. Unlike the other amines, its action is irreversible, it is not oxidized by amine-oxidase, and is excreted unchanged in the urine. Like other drugs of the deliriant group, its effect consists of a combination of dysoxic (depressant) and dysglycic (excitant) symptoms.

When mescaline is administered in dosage of 0.2 to 0.5 grammes to a normal subject, it produces an acute encephalopathy which lasts from 10 to 24 hours, and is almost exactly similar to an acute dysglycic state in clinical features. The drug possesses three striking peculiarities which distinguish it from the other deliriant alkaloids: the symptoms occur in a setting of clear consciousness, without disorientation or impairment of the intel-

lectual faculties, unless the dose has been very large—a fact to which attention was first drawn by Rouhier in his famous monograph: the symptoms occur in intermittent paroxysms with intervening periods of apparent normality and complete lucidity; and it has a specific action on the sleep-centres, producing absolute insomnia, unlike morphine, cannabis, and other narcotics, whose effect is one of stimulation, followed by depression and finally sleep.

The psychical phenomena are manifested in the sensory, affective, ideational, and motor fields. From the psychopathological aspect, its characteristic action is that of bringing into consciousness the submerged complexes and subconscious desires of the subject in the form of hallucinations, delusions, and other typically encephalopathic symptoms. In other words, the thought-processes during the intoxication are katathymic in type, just as in the metabolic encephalopathies. Thus, the sensory phenomena are always determined by the repressed complexes and phantasy-life of the particular individual, and the resultant clinical picture varies greatly in different subjects according to the personality and temperamental make-up; thus, in schizoid individuals, it is typically dysglycic in form, and in cyclothymics resembles more closely the manic-depressive type of dysoxic state.

The striking similarity between the mescaline and the natural metabolic encephalopathy will at once become apparent as regards these four peculiarities—clear setting of consciousness, remissions and exacerbations, insomnia and katathymic thinking.

The ingestion of an intoxicating dose produces the following train of symptoms. After a latent interval of fifteen to twenty minutes, marked dilatation of the pupils sets in, the pulse accelerates, and a state of general hyperreflexia occurs. Subjectively, the subject experiences a feeling of oppression in the occiput, throat, and praecordium, accompanied by a peculiar sensation of uneasiness, apprehension, and motor restlessness, with increasing slowness and difficulty in thinking. Moderate nausea, occurring in paroxysms, is an invariable feature.

The sensory phenomena next appear in the form of vivid hallucinations of all senses, chiefly visual, but also occurring in the auditory and other modalities. The visual form consists of coloured visions of indescribable splendour, varying from simple geometrical patterns to complex and elaborate scenes and figures so bizarre in form as to be quite indescribable in ordinary language.

The auditory type consists of musical sounds, or of voices speaking to the subject in a highly condensed and symbolic language. The somatic hallucinations take the form of bizarre paræsthesias referred to all parts of the body; these are of typical dysglycic form, being variously interpreted by the subject as electrical influence, interference by wireless, thought-reading, supernatural beings, and so on, which often lead to the formation of delusions of persecution and reference. The hallucinations may thus be of hedoniphronic or nociphronic type, and, like those of encephalopathics, appear perfectly real to the intoxicated person. Synæsthesias, or combined sensations partaking equally of visual, auditory, and somatic characteristics, are a typical and striking clinical feature of the experience.

In addition to the hallucinosis, a characteristic and extraordinary disturbance of visual and auditory perception is found, in which the appearance of objects, the sound of other people's voices, and their facial expressions, become distorted in a remarkable manner. At the same time, the subject experiences a feeling of morbid suspicion and exaggerated self-awareness, which, together with the illusions and hallucinations, leads readily to the formation of ideas of reference and persecutory delusions exactly similar to those found in the dysoxic and dysglycic states.

Disturbances of thought include extreme retardation with slowing of the stream of thought, flight of ideas, disconnection, bizarre ideas, feelings of passivity, and the peculiar disorder of conceptual thinking and associational disturbance which is so characteristic of the dysglycic encephalopathies.

The sensorium and intellectual faculties remain clear throughout the intoxication, and disorientation in space and time does not occur unless the dosage has been of the order of 0.5 grammes or more. There is always a peculiar disorder of temporal and spatial perception, in which time seems to be enormously prolonged and space greatly enlarged and distorted.

In the personality-sphere, there is a marked feeling of unreality and depersonalization, with illusions of multiple personality and transformation of the subject's identity.

On the motor side, the most striking symptom is katatonic stupor, which is seen in mescaline intoxication in its most extreme and classical form. It is in all respects identical with that found in the katatonic dysoxias, with flexibilitas cerea, posturing, bizarre grimaces and mannerisms, fatuous laughter and smiling, and impulsive outbursts of excitement and purposeless activity

It is often associated, as in dysoxia, with ideas of death and self-reproach.

It differs from the katatonia of bulbocapnine-poisoning in that muscular power and voluntary movement remain unimpaired throughout the course of the intoxication. Also, in contrast to what is found in alcoholic intoxication, ataxia, dysarthria, slurring of speech and defects of postural sense do not occur ; in other words, the action of the drug is confined entirely to the highest cortical levels, the cerebellar centres and lower motor systems being unaffected.

The affective reaction is characteristically one of intense euphoria, in which property mescaline far surpasses the opium and cannabis drugs ; but it often varies from complete apathy to intense depression, associated with ideas of unworthiness and self-reproach, agitation, and feelings of indescribable fear and panic. This reaction is most commonly seen at the commencement of the intoxication. Affective incongruity and bizarreness of typical dysglycic form are very commonly found.

The vegetative symptoms consist of intense mydriasis, nausea, anorexia, sexual frigidity, and absolute insomnia ; the specific sleep-inhibiting property of the drug has already been referred to as characteristic. Otherwise, the physical concomitants are those of any acute toxæmia, as in the fulminating type of encephalopathy—namely, earthy pallor, dry lips, coated tongue, scanty and highly concentrated urine, constipation, dehydration and suppression of the normal cutaneous secretions.

From the physiological point of view, the effects of mescaline may be regarded as a mixture of stimulation and depression. The most probable explanation of the mental symptoms would appear to be that of a selective action of the drug on the highest cortical levels and diencephalic-thalamic centres, while the lower parts of the brain-stem—midbrain nuclei, cerebellum, and medullary centres—escape. Thus, the katatonic phenomena are undoubtedly due to its action on the frontal lobes and their connections with the motor and premotor areas. The visual, auditory, and somatic hallucinations are the results of the action on the glycolytic functions of the cells of the visuo-psychic, acoustico-psychic, and somatico-psychic sensory areas respectively ; and the ideational and thought-disturbances are due to an acute upset of the oxidative and glycolytic mechanisms of the neurons composing the cortical association-systems and other groups of cells concerned with the higher thought-processes. The

affective changes are probably due to its action on the thalamic centres and their cortical connections, and the personality-disorder and disturbance of the reality-function would seem likely to be part of the same mechanism. The vegetative disturbances are due partly to the general toxæmia produced, and partly to the atropine-like effect of the drug on the parasympathetic system.

The above is necessarily only a brief and condensed account of the psychical phenomena produced by this remarkable drug. It would not be possible in a work of this length to deal fully and in detail with all the aspects of its varied symptomatology, and the many interesting questions in psychopathology and cerebral physiology which it raises. Before, however, leaving the subject of drug-encephalopathies, some of the more important points in this connection will be briefly discussed.

It will be evident from a consideration of the symptomatology described above that this alkaloid is unique in its power to produce a clinically typical dysoxic-dysglycic syndrome under experimental conditions in the normal person. There are, however, certain differences between the naturally occurring and artificially induced encephalopathies which should be stressed at this point.

The first is that the mescaline experience represents the organisms' reaction to a sudden and overwhelming dose of a toxic agent—an occurrence which is rarely found in nature, at any rate in the case of metabolic disorders. Much more commonly, a metabolic encephalopathy is the end-result of long-continued action upon the organism of one or more noxious agents, such as fatigue, unresolved mental conflicts, or mild forms of toxæmia. It is well-known that a typical encephalopathy can be induced as the result of continuous ingestion over a long period of small amounts of toxin, as is exemplified by such conditions as alcoholic hallucinosis and delirium tremens, cocaine paranoia, and the mental sequelæ of chronic hashish-intoxication. As mescaline is not a habit-forming drug, no literature dealing with the subject of chronic mescalinism is available ; it would certainly be interesting to try the effect of long-continued ingestion of the drug in small doses on the normal human being. The possible results of such an experiment would, of course, be purely speculation in the present state of our knowledge, but it seems probable, in view of what is found with alcohol and other poisons, that the end-result would be a chronic hallucinatory-paranoid encephalopathy.

The second difference is in the type of hallucinosis found. In the case of mescaline intoxication this is chiefly of the visual form, whereas in the classical types of metabolic encephalopathy it is predominantly aural. It is generally stated in most psychiatric text-books that coloured visual hallucinations are typical of organic and toxic states rather than of the true " schizophrenic " (i.e., dysglycic) conditions, whereas complex aural hallucinations are typical of the so-called " psychogenic " conditions (under which heading the metabolic encephalopathies are included). This has led to the generally accepted view that the mechanism of the two classes of cerebral disorder is essentially different, and that a fairly sharp distinction can be drawn clinically between the " schizophrenic " and " toxic-confusional " diseases. Support has been lent to this view by the oft-repeated assertion that in the former condition a setting of clear consciousness is the rule, whereas in the latter confusion and disorientation are always found. This has been one of the principal arguments advanced against the organic view of causation of the metabolic encephalopathies.

This argument is, in the opinion of the writer, definitely invalidated by the following facts. In the first place, the phenomena of mescaline poisoning, as already pointed out, occur in a setting of clear consciousness with unimpaired intellectual functions ; moreover, typical complex aural hallucinations of "schizophrenic " type are found in this conditon. In many acute dysoxic and dysglycic states, on the other hand, visual hallucinosis of the bizarre mescaline type is a common finding, while clouding of consciousness is of frequent occurrence in the acute phase both in dysoxic and dysglycic encephalopathy. In some of the more fulminating types, indeed, the visual appears often to be the predominating form of hallucinosis, and may completely replace the aural type. It is interesting to note that in this connection, the writer has on many occasions obtained from dysglycic patients, when rendered accessible by means of amytal narcosis, descriptions of typical mescaline-like visual experiences undergone during the acute stage of their disorder. It is also worthy of note that not a few acute encephalopathies, which commence as classical " toxic-confusional " states, fail to undergo remission, the symptoms gradually becoming more " schizophrenic " in type, so that the end-result is a typical " schizophrenic " encephalopathy.

Again, in certain forms of acute hysterical twilight-state, a

bizarre form of pseudo-hallucinosis of visual type is not uncommon ; and these conditions are generally held to be of entirely psychogenic origin.

It would appear, therefore, that there is strong evidence for believing that the underlying mechanism of the drug-induced, toxic-confusional, and metabolic encephalopathies is essentially the same—namely, an acute upset of the oxygen-glucose metabolism of the brain-cells, and that the difference between them clinically is simply one of degree, according to the acuteness or otherwise of the symptoms. The close resemblance between the physical symptoms found in these conditions would appear to lend additional support to this view. This, however, is not the same as postulating a toxic amine as the causal agent in all cases of encephalopathy, as has been suggested by some workers ; the toxic amine hypothesis will now be briefly discussed in relation to the disturbances of nitrogen-metabolism which have been found in certain katatonic forms of encephalopathy.

The toxic amine hypothesis supposes that the symptoms of encephalopathic patients are due to the action on the brain-metabolism of a neurotoxic amine, possibly chemically allied to mescaline, generated in the body as a result of defective detoxication by the liver. In support of this theory, it has been shown that certain amines found in the intestinal tract have a similar effect to that of mescaline on neuronal metabolism, and that normally those amines are detoxicated in the liver by the enzyme amine-oxidase ; moreover, in some forms of encephalopathy abnormalities of hepatic functions have been demonstrated, to which further reference will be made. Against this hypothesis, however, we have the fact that no-one has yet succeeded in demonstrating the presence of such a toxin in the blood of encephalopathic patients, while the anomalies of liver-function are by no means constant ; although it must be admitted that no satisfactory method has up to now been devised for the detection and estimation of toxic amines of the mescaline type in the blood.

In connection with the theory of disturbed nitrogen-metabolism, the work of Gjessing is of considerable interest. His investigations were carried out on patients suffering from the form of dysoxia known as periodic catatonia, which is characterized by normal intervals with regularly occurring phases of acute stupor of the katatonic type. He found that the stuporose periods were associated with phases of nitrogen-retention ; the nitrogen-retention preceded the onset of the katatonic symptoms,

and it was found that a normal nitrogen-balance with concomitant mental improvement could be produced by the exhibition of thyroid extract in large doses. On the other hand, increasing or diminishing the amount of protein in the patient's diet did not influence the rhythm of the mental disorder. It was concluded that the metabolic disturbance was not secondary to the mental change, nor was the mental disorder immediately caused by the metabolic change, but that both were secondary to a primary cyclical alteration in the endocrine balance. The metabolic changes were found to disappear in patients who showed a good response to electroanoxia, but persisted in those who failed to show improvement mentally with this form of therapy.

In conclusion, therefore, it may be said that no direct evidence of the presence of toxic amines in the blood of encephalopathic patients has yet been found, and that it would appear more probable that the changes in nitrogen-metabolism are simply part of of the general metabolic disturbance, which is primarily of the glucose-oxygen mechanisms of the cerebral cells.

It is, however, worthy of note in this connection that in certain conditions of endogenous toxæmia, such as uræmia and hypersensive states, in which there is a disturbance of nitrogen-metabolism, mental symptoms of encephalopathic type not uncommonly occur; these conditions include hallucinatory, confusional, and acute maniacal states, which in many respects bear a close resemblance in clinical features to the acute forms of metabolic encephalopathy.

(4) The Clinical Evidence for a Metabolic Basis.

Physical signs pointing to a generalized disturbance of the metabolic functions are found in a large proportion of patients with metabolic encephalopathy. They vary from the gross signs of acute toxæmia seen in the acute confusional forms to the milder and less dramatic features seen in the chronic and degenerating forms.

In the case of the former, reference has already been made to the classical signs of acute generalized toxæmia; the acutely confused patient, with unhealthy-looking muddy skin, wasting, dehydration, foul breath, coated tongue and sordes-encrusted lips, tachycardia, and unnaturally brilliant eyes, provides a clinical picture which once seen is not easily forgotten. In the chronic forms, such features are, of course, absent, but in their place are frequently seen the signs of progressive physical degen-

eration, such as unexplained wasting, progeria, aerocyanosis, and regressive changes in the endocrine system.

Derangements of hepatic function as shown by the occurrence of nitrogen-retention in the katatonic forms have already been referred to in connection with the work of Gjessing. In addition, abnormalities have been found in urea-synthesis and esterization of cholesterol, possibly as the result of pathological fermentative processes in the liver. In many cases, tests of liver-function by the administration of benzoic acid show diminished output of hippuric acid in the urine, indicating a derangement of the normal detoxicating mechanisms of the liver. In chronic cases, a lowered value of the blood-lipoids is also a common finding. It has been shown by Golla that there is a decreased response of the respiratory centre in the encephalopathic patient to the normal carbon dioxide stimulus, with a tendency towards shifting of the PH with acidosis, while shallow respiration with diminished air-intake is not uncommonly found. The respiratory disturbance and upset of the acid-base equilibrium, with decrease in the circulatory rate and increased tonus of the parasympathetic system, and correspondingly lowered activity of the sympathetic, are changes similar to those seen in the normal subject during sleep. In this connection it may be noted that, as the result of neurometabolic therapy, the opposite reaction is produced—namely, alkalosis and increased tonus and activity of the sympathetic system.

The carbohydrate-metabolism also shows frequent abnormalities. Thus, Meduna has demonstrated an insulin-antagonizing substance in the blood of dysglycics, while many cases of the stuporose dysoxic type also exhibit a marked resistance to the action of insulin ; in these patients, doses of 150 units or more often produce very little effect beyond slight somnolence and sweating, with concomitant failure to improve mentally. Abnormal response to insulin of the blood-sugar curve is also a not uncommon observation.

In the blood of katatonic and hyperkinetic patients abnormally high values of bisulphite-binding substances, pyruvic, and lactic acids may be found ; the importance of the last two substances in cerebral glucose metabolism has already been discussed. In quiet and apathetic patients, on the other hand, these values are normal. Carbohydrate tolerance tests with lactic acid and adrenalin frequently also show abnormal results.

Vasomotor anomalies, such as acrocyanosis, have already been

mentioned. A condition of chronic constriction of the cerebral capillaries, resulting in decreased permeability and diminished blood-supply to the brain, have also been demonstrated ; this is the theoretical basis of the histamine-insulin therapy introduced by Hill, the object of which is to obtain an increase of vascularity and blood-supply to the cerebral tissues, by making use of the powerful vasodilator action of histamine.

Occasional abnormalities of the cerebrospinal fluid, such as increase of the protein-content, have been reported by some workers, but these are usually very inconstant.

In some acute katatonics, sudden death may occur, associated with fatty degenerative changes in the liver. This is found especially in some fulminating types of dysoxia and dysglycia ; in the form known as Scheid's cyanotic syndrome, pyrexia, generalized severe cyanosis, stupor, and rapidly fatal physical deterioration are the striking features. These acute malignant forms bear a striking resemblance in their clinical signs and course to acute suprarenal failure, and certainly suggest an acute metabolic upset of unusual severity.

In the simple depressive form of dysoxia, diminution of the salivary secretions and abnormal variations in body-temperature, have been described, which are strongly suggestive of parasympathetic dysfunction.

One of the most striking characteristics of the encephalopathic patient as compared with the normal subject is the response to the administration of drugs. Generally speaking, this consists of an abnormally high resistance to all drugs which act on the cerebral functions, whether stimulants or narcotics. All those who have had much to do with the treatment of encephalopathic patients know this well ; thus, an acutely excited or agitated depressed patient may hardly be affected at all by a dose of a powerful hypnotic which would be sufficient to render a normal person comatose within a short time. Stuporose and apathetic cases, on the other hand, show little or no response to large doses of powerful sympathetic stimulants, such as thyroid or benzedrine, which would produce toxic effects in a normal subject. Thus, apathetic dysglycics and dysoxics will often tolerate thyroid in dosage of up to 15 grains daily, with mental improvement and no untoward side-effects. The rarity of dysglycia in combination with thyrotoxicosis is well-known ; and these facts appear to be strong evidence in favour of the hypothesis of defective function of the sympathetic system in this disease. In the case of

acutely depressed and retarded patients, benzedrine in large doses produces no improvement in the mental symptoms, in marked contrast to what occurs when it is administered for fatigue-states and minor neurotic depressions in the non-encephalopathic person.

The effects of inhalation of gases provide another example of the abnormal metabolic reactions of encephalopathic patients, and of the generally lowered sympathetic response. Thus, there is a lowered autonomic response to the inhalation of oxygen when under stress, and the same is the case with the administration of insulin. The lowered response of the respiratory centre to the carbon dioxide stimulus has already been mentioned. In the normal person, the inhalation of carbon dioxide-rich mixtures simply produces drowsiness and transient mental confusion ; in the inaccessible and stuporose encephalopathic, however, it often produces a temporary and dramatic abolition of the stupor, the patient becoming suddenly lucid, co-operative and sensible. The same is the case with intravenous barbiturate administration ; and in both cases it seems likely that the temporary mental improvement is due to a sudden inhibition of the abnormal cerebral metabolism by the pharmacological agent.

The response of the encephalopathic to euphoriant drugs is also characteristically different from that of the normal individual. The general rule is that drugs, which in a normal person would produce an affective change in the direction of euphoria, are either without effect in the encephalopathic, or else simply intensify the symptoms already present. Thus, the weaker euphoriants, such as morphine, produce little or no amelioration of the depression in simple dysoxia, while the more powerful, such as cannabis and mescaline, produce a marked intensification of the depression, retardation, agitation and other dysoxic features. In other words, the affective response is the exact opposite of what is found in the normal subject. In chronic dysglycics, disagreeable hallucinations are to some extent modified in that they are made more pleasant, the affective change being in the direction of perplexity, anxiety, and euphoria.

These results are in accordance with what would be expected if, in the encephalopathic, the cerebral metabolic processes were different from those of the normal subject. Thus, in depressive dysoxia, it would be expected that the administration of such an agent would produce an amelioration of the depressive symptoms, if the disorder were a purely psychogenically determined con-

dition. In point of fact, the opposite occurs, so that the only logical conclusion is that the underlying disorder is a dysfunction of the cerebral metabolic processes.

The final piece of evidence in support of the metabolic hypothesis is provided by the non-response of the encephalopathies to psychotherapeutic measures and their favourable response to neurometabolic therapy, which exerts its effect by virtue of direct action of the oxygen-glucose metabolism of the brain and the autonomic activities of the diencephalic centres.

(5) The Evidence for an Organic Basis.

General medicine provides some noteworthy examples of metabolic disorders which in their early stages show no gross organic changes, but which, if allowed to progress untreated, ultimately produce widespread degenerative lesions of an undoubtedly organic type. Well-known examples are provided by diabetes mellitus, thyrotoxicosis, and essential hypertension; thus, in the last-named condition, no gross changes are apparent in the early stages, but, in the course of years, characteristic organic changes become evident, such as hypertrophy of the cardiac muscle, and sclerotic lesions of the blood-vessels and kidneys. In the same way, metabolic encephalopathy in its early stages shows no gross organic changes but in chronic deteriorated patients organic degenerative changes are found in the brain and other organs. These lesions are, of course, not specific or peculiar in any way, but are simply the end-results of a degenerative process due to the long-standing metabolic disturbance.

Mention has already been made of the signs of general physical degeneration seen in many chronic hospital patients in civil practice, such as wasting, progeria, and other signs of a generalized metabolic and endocrine deterioration. The work of Mott, and more recently, that of Hemphill on the degenerative and endocrine changes found in chronic dysglycia is well known in this connection. Mott demonstrated that in chronic deteriorated cases of this disorder diffuse degenerative changes were present in the cerebral cortex, such as neuronal degeneration, atrophy, neuronophagy, and proliferation of the neuroglial elements. In association with the cerebral lesions, degeneration of the endocrine glands was demonstrated; this was found especially in the testes, which exhibited degeneration of the seminferous tubules, arrest of spermatogenesis, and generalized atrophy.

In the vascular system, a general state of hypoplasia has been described, with narrowing of the great vessels and cardiac underdevelopment in chronic deteriorated patients.

These changes are of the type which would be expected in a chronic metabolic disorder, and can, to a certain extent, be correlated with the permanent and incurable mental residua found in the chronic encephalopathic patient. Thus, it is possible that the apathy and emotional deterioration are due to degenerative changes in the thalamic and diencephalic nuclei, or their connections with the frontal cortex ; it may be noted in this connection that it is these fibres which are divided in the operation of prefrontal leucotomy, the object of which is the reduction of intrapsychic tension. Similarly, persistent aural and visual hallucinosis can be correlated with irreversible changes in the cells and fibres of the acoustico-psychic and visuo-psychic areas respectively ; fixed delusions and thought-disorder with changes in the higher association-neurons and tracts, and katatonic motor disorders with degenerations in the frontal lobes and fronto-thalamic connections.

It should be understood, of course, that the pathological changes described are a diffuse and widespread change extending over the whole cortical system, and not circumscribed neurological lesions of the type which give rise to the classical motor and sensory syndromes of the neurological text-books.

(6) Some Present-Day Theories of Causation.

Before concluding this chapter on the pathophysiology and morbid anatomy of the encephalopathies some of the theories which have been recently advanced to explain the mechanism of these conditions will be briefly reviewed.

The psychogenic theory, which is upheld by a large number of leading psychiatrists, supposes that the symptoms of encephalopathy can be explained entirely by internal psychic conflicts and maladjustments as the result of various stresses, without postulating any sort of organic disturbance, metabolic or otherwise. In other words, they believe that abnormal mental function of a gross kind can obtain in the presence of a nervous system which is organically normal.

The writer does not deny that metabolic encephalopathies can be precipitated as the result of internal psychic stress or environmental difficulties in constitutionally predisposed individuals ; this is made clear in the chapter on ætiology. What in the

writer's view the exponents of the psychogenic theory fail to do is to differentiate between the precipitating factors and the actual disturbance underlying the morbid symptoms.

The objections to the psychogenic theory are at once obvious. In the first place, they completely fail to explain the gross disorders of the thought-processes, conduct, and sensation—such as hallucinosis and dyssymbole for instance—which can only be induced experimentally by the administration of mescaline. They do not account for the undoubtedly organic type of mental deterioration found in chronic encephalopathics, and the degenerative changes which occur in the brain and other organs ; nor do they explain adequately the autonomic changes associated with the mental symptoms. But the most serious objection of all, which rules out entirely a purely psychogenic causation, is the non-response of these conditions to psychotherapy and their response to the purely physical and biochemical procedures of neurometabolic therapy. In the writer's view, this last fact renders all purely psychogenic theories completely untenable.

Other theories which have been recently put forward are a disturbance of the autonomic system, a primary endocrine disorder, and an extra-cerebral toxin, possibly a toxic amine, formed as the result of auto-intoxication or hepatic dysfunction.

The exponents of the autonomic theory adduce as evidence the autonomic disturbances found in a large proportion of cases, and the evidence of a general non-responsiveness and underactivity of the sympathetic system. Reference has already been made to these features in the discussion of the biological changes found in encephalopathic patients.

The objections to this theory are the absence of characteristic autonomic disturbances in a large proportion of cases, and the fact that in many medical conditions of gross autonomic dysfunction—for example, Raynaud's disease and the vaso-vagal syndrome of Gowers—mental symptoms of encephalopathic type are absent. Again, the exhibition of such potent autonomic stimulants as benzedrine, carbaminoyl-choline, and histamine is without benefit in these disorders ; indeed, as previously pointed out, stuporose and depressed cases are often actually made worse by the administration of benzedrine. Also, in both the anoxic and hypoglycæmic forms of therapy, the most important factor in producing mental improvement appears to be cerebral anoxæmia and hypoglycæmia, since cases in which the autonomic response is minimal often do well in spite of this. These facts, in

the writer's view, would seem to be definite evidence against the theory of an autonomic disturbance as the primary ætiological factor.

The endocrine theory, which has come into prominence as a result of the researches of Mott and his collaborators, is open to the same objections. The fact that degenerative changes in the reproductive organs are found is no proof that they constitute the basic pathological lesion ; it seems more probable that they are simply degenerations secondary to a chronic generalized metabolic disturbance. Again, although anomalies of the endocrine system do occur in a considerable proportion of cases, an equally large number show no such abnormalities ; also, in many cases of gross conditions of endocrine dysfunction, such as eunuchoidism, the pituitary syndromes, and thyrotoxicosis, mental symptoms do not occur. The rarity of thyrotoxicosis in association with metabolic encephalopathy has already been referred to in this connection, while no definite clear-cut endocrine syndrome has ever been demonstrated in association with either the dysoxic or dysglycic form of encephalopathy. Finally, therapeutic trials with the new and highly active synthetic androgens and oestrogens in cases of metabolic encephalopathy have so far produced inconclusive results. Hemphill and his co-workers found that slight improvement was evident in some chronic cases with these preparations, but that it was in no way comparable with the results obtained with neurometabolic therapy. These facts would suggest that the endocrine changes are a secondary rather than a primary ætiological feature.

Reference has already been made to the toxic amine hypothesis in connection with nitrogen-metabolism and mescaline encephalopathy. The principal objection to this theory up to now has been the failure of its supporters to demonstrate the presence of such a toxic body in the blood of encephalopathic patients. As Richter points out, the work of Gjessing cannot be adduced in support of the amine theory, since it is found that, even in the recurrent katatonic form, the changes in nitrogen metabolism are by no means constant ; thus, it is found that some such patients show a state of positive nitrogen-balance even while in the active stage of their disease, while in others the reverse is the case. Furthermore, the nitrogen-retention observed applies to all the protein-degradation products found in the urine, which suggests that the underlying disturbance involves the total protein-katabolism, and not merely a single intermediate meta-

bolite which might be the parent-substance of a toxic amine. These facts support the view that the metabolic disturbance is primarily one of the oxygen-glucose metabolism, the nitrogen disorder being a purely secondary feature.

(7) Summary and Conclusions.

A consideration of the foregoing facts strongly suggests that the causal factor in the metabolic brain-disorders is a profound and generalized upset of the whole metabolism, originating in the cerebral cells and affecting through the medium of the hypothalamic-diencephalic complex the whole of the endocrine and autonomic systems. The morbid change may be considered as primarily affecting the oxidizing and glycolyzing cells of the cerebrum, and, secondarily, through the cortico-diencephalic and thalamic connections, those centres which control the autonomic and endocrine functions. The lower centres—midbrain, cerebellum, and medullary nuclei—escape, thus explaining the absence of a characteristic neurological syndrome in association with the mental symptoms.

The mental symptoms of the metabolic encephalopathies can be adequately explained on the basis of a diffuse cerebral metabolic process of this kind, and the observed clinical and experimental evidence in support of the hypothesis has been set forth and fully discussed in the foregoing paragraphs.

The physical phenomena, that is to say, the autonomic, endocrine, toxic, and degenerative organic changes—can also be accounted for on the cerebral metabolic theory. None of these hypotheses alone—whether psychogenic, endocrine, degenerative, autonomic, or toxic—provides an adequate explanation either of the clinically observed facts or of the therapeutic effects of neurometabolic therapy.

The mere fact that such a process cannot be directly demonstrated is no proof that it does not exist, and cannot be adduced as an argument against the metabolic theory. General science provides many striking instances of this; thus, for example, atoms, molecules, and ultramicroscopic viruses are invisible even under the most powerful microscopes, yet no-one doubts their reality, because indirect evidence of their existence is provided by observation of the effects which they produce; and the observed facts can only be explained on the theory of their existence as real entities. Similarly, at the end of the seventeenth century, Malpighi correctly prognosticated the existence of minute organ-

isms as the cause of infections, but it was not until nearly two hundred years later that microscopes sufficiently powerful to prove the correctness of his theory became available. To bring the analogy still closer in the case of the metabolic diseases, the existence of an anti-diabetic principle was demonstrated indirectly by the experiments of Mering and Minkowski long before insulin was actually isolated as a definite chemical body by Banting and Best. In the same way, the existence of metabolic encephalopathy as a definite disease-entity can be shown by observation of the clinical and biochemical facts, although it cannot be demonstrated directly.

The other argument which has been advanced against the metabolic theory is the apparent absence in a large proportion of cases of any evidences of abnormal metabolic activity. This is, of course, true especially in the great majority of chronic mental patients; but in the writer's view it cannot be advanced as a conclusive argument against the theory, since it is to be expected that such metabolic abnormalities would be detectable only in the early and active phase of the disorder. In the chronic and quiescent stage, however, when the active process has burnt itself out, so to speak—as in the chronic delusional dysglycias—one would not expect to find evidence of abnormal metabolism; just as, for instance, one would not expect to find evidence of active spinal cord inflammation in an old case of anterior poliomyelitis, but only the signs of chronic muscular wasting and paralysis.

In those cases which are still in the active stage but in which metabolic changes are apparently absent, it is probable that these abnormalities are too slight to be detectable by the methods at present available. Stress has already been laid upon the extreme sensitivity of the cerebral cells to very slight changes in their biochemical milieu, especially as regards oxygen and glucose supply. It is more than likely, therefore, that in many cases of metabolic brain-disease the metabolic changes are present, but so slight as to be undetectable by present-day biochemical methods. It is equally probable, however, that with the advance of our knowledge within a few years time instruments and techniques will have become perfected by means of which direct observation of the cerebral metabolic processes will be possible, so that our understanding of the nature of these disorders will be advanced beyond anything conceivable at the present time.

CHAPTER III

III. ÆTIOLOGICAL FACTORS IN METABOLIC ENCEPHALOPATHY.

(1) General Considerations.

The essentially organic nature of the metabolic encephalopathies has been indicated in the previous chapter, and clinical and experimental evidence presented to show that the type of mental symptomatology found in these conditions can only be explained adequately on the theory of a cerebral metabolic disturbance. This is not to suggest, however, that purely psychological factors play no part in their genesis, or to underrate the importance of emotional stresses and maladjustment as precipitating factors ; nor does the hypothesis of metabolic upset of the nervous system leave out of account the importance of heredity and constitutional make-up.

The clinical experience of recent years has tended to lay increasing emphasis on what is generally termed the psychobiological approach to the problems of disease, that is to say, the concept of mind and body as a single and integrated whole, and not as separate entities each in its own watertight compartment. This method of approach has become especially important in connection with the problems of clinical psychiatry in recent years.

It will be convenient to consider first the question of purely emotional and mental factors in the causation of these disorders by asking the question ; Is it possible for such emotional disturbances alone to give rise to an organic metabolic change in the organism, which can progress to irreversible structural damage ? The answer to this question is, undoubtedly, yes.

It is well-known that the interdependence of mind and body is an extremely close one, and physiologists have demonstrated, both in the laboratory animal and in the human subject, that emotional shock and stress can give rise to a definite sequence of autonomic and metabolic changes in an otherwise organically healthy organism. Thus, in the experimental cat stimulated by the sight of the dog, we see all the phenomena of the acute emotional crisis ; erection of the hairs, dilatation of the pupils, tachycardia, hypersecretion of adrenalin, and other signs of sudden and increased activity of the sympathetic system are the somatic concomitants of the acute fear-reaction. The same type of

response is seen in the human subject as the physical signs of acute emotional stress and anxiety-states.

Similary, general medicine furnishes well-known examples of an organic condition arising in an apparently healthy subject as the result of prolonged psychological stress. Examples of such condition are ; the onset of hyperthyroidism in females of the anxious, worrying type following a period of prolonged anxiety ; the association of hyperpiesis with personalities of the over-active, extroverted, or worrying temperament ; and the development of peptic ulcer, mucous colitis, and other gastro-intestinal disorders under conditions of chronic emotional strain ; while certain forms of skin-disease, such as psoriasis and lichen planus, are considered by many to be determined by psychological factors. It is worthy of note that all the conditions listed above are generally believed to be, like the encephalopathies, examples of metabolic disorders, and it seems probable, if not certain, that the somatic changes in such conditions are brought about through the medium of the autonomic nervous system.

It is therefore reasonable to suppose that in certain individuals an acute cerebral metabolic upset can be produced as the result of psychic stress—either sudden and overwhelming, as in the acute forms which come on after exposure to battle-stress, or chronic and progressive, as is commonly found in civilian practice, where the encephalopathy is the end-result of prolonged efforts on the part of the patient to cope with mental conflicts and environmental maladjustments. Not all cases, of course, who are subjected to such stresses will go on to metabolic encephalopathy ; and it is here that the second factor, that of constitutional makeup and heredity, comes into play. It appears probable that persons whose heredity and psychosomatic constitution are sound can go on indefinitely under stress, with a partial or complete adjustment and without suffering an acute metabolic breakdown ; whereas in those who are handicapped by inferior psychosomatic constitution the cerebral metabolism is more precariously balanced, and liable to break down completely when subjected to excessive stress.

It will be apparent from a consideration of these facts that the metabolic hypothesis is in no way incompatible with the theories of psychological maladjustment propounded by the earlier schools of thought, and that the psychogenic and metabolic theories can be reconciled completely. Where the former school went astray, however, was in failing to draw a distinction between

the precipitating factors and the actual disease-process resulting from them ; since in metabolic encephalopathy, as in the other conditions mentioned above, by the time the patient comes to the psychiatrist for treatment the precipitating stresses have largely ceased to operate, and an established organic process is present—in other words, the patient has now ceased to be a psychotherapeutic problem, and has become a case for physical and pharmacological forms of therapy. This is, of course, not synonymous with saying that psychotherapeutic methods should be ignored, any more than the psychological aspects should be neglected in the case of a patient suffering from a purely medical or surgical condition.

In conclusion, therefore, we may say that the syndrome of metabolic encephalopathy is a reaction of the whole organism to environmental stresses and changes, and may be precipitated by a large number of different agencies, such as mental strain, physical exhaustion, toxins, infections, and so on ; exactly in the same manner as, for example, the syndrome of hepatic cirrhosis can be produced by the action of various different agents—infection, alcohol, constitutional degenerative diseases, etc. The important fact is that, whether the precipitating cause be toxic, psychogenic, or physical, the resultant morbid change, clinical course, symptomatology, and response to therapy are essentially the same, with minor modifications according to the constitutional and hereditary make-up of the particular case under consideration.

(2) Ætiological Factors.

From the standpoint of ætiology, the metabolic brain-diseases may be divided into a primary, or endogenous, and a secondary, or exogenous, group. The primary group includes those encephalopathies which arise without obvious precipitating cause, examples of which are the manic-depressive form and the simple type of malignant dysoxia ; while the secondary group includes those which arise as reactions to various kinds of external stress, such as battle-experiences, climatic conditions, or the toxins of acute infections, to name some of the common precipitants encountered in military practice.

The age-incidence and main types of metabolic disorder seen in military psychiatric hospitals have already been considered in a previous chapter. For both the dysoxic and dysglycic forms of encephalopathy, the ætiological factors are the same, psycho-

logical stress of various kinds being the commonest of all ; these will be considered last.

Of infectious diseases, the same types which are found in civilian practice may act as precipitating causes. Two of these—malaria and infective hepatitis—are of particular importance, especially in cases invalided from tropical and sub-tropical theatres of operations.

Malaria has been found to be an important precipitating factor in a considerable proportion of post-toxic encephalopathies. It is of special significance, as it is not uncommonly brought home in the quiescent form by men who have had a previous attack with inadequate treatment. A simple benign tertian attack is rarely productive of encephalopathic symptoms ; more commonly, the breakdown sets in when the patient is in a state of debility following a succession of relapses or in cases of the acute cerebral form of the disease. The onset of the metabolic symptoms may be sudden, with acute delirium and hallucinatory confusional features during the febrile phase ; it may clear up spontaneously and completely in a matter of days or weeks, or may persist after the malarial symptoms have cleared up, and progress to a typical encephalopathy of either dysoxic or dysglycic type. In the forms with a subacute onset, the mental symptoms usually commence when the patient is in the convalescent stage, and is in a state of asthenia and exhaustion. The patient, instead of having a normal convalescence, becomes gradually depressed, listless, and lethargic ; later, persistent insomnia, ideas of reference and hallucinosis begin to make their appearance. The end-result is usually a dysoxic encephalopathy of the malignant type, and not uncommonly a sudden suicidal attempt may be the the first indication of the mental change in this type of case.

Infective hepatitis, which has been epidemic both in this country and in the Mediterranean and Middle East areas during this war, may set off a metabolic encephalopathy in the same way. The clinical history is similar to that described for the post-malarial form. In the case of infective hepatitis, the general tendency is for the metabolic symptoms to take the form of a depressive dysoxic syndrome, acute dysglycic reactions being less common than in the post-malarial forms.

Of chemical poisons, drugs of addiction and the common industrial poisons are practically never encountered, as would be expected. The writer has seen one or two cases of metabolic encephalopathy following exposure to petrol fumes, as the result

of accidents while unloading petrol tankers and tenders. These cases differ in no respect from the ordinary forms in clinical course and symptomatology.

Among therapeutic drugs, one which has become increasingly used recently can be definitely incriminated as a causal agent in some cases of encephalopathy. This is mepacrine, or atebrine, the synthetic anti-malarial which has practically replaced quinine during this war as the standard treatment for malaria. It has long been known that in some individuals a definite train of mental symptoms is produced by the administration of this drug. The syndrome includes mental confusion, elation, insomnia, hallucinosis, and other features of an acute dysglycic state; this may either clear up completely on withdrawal of the drug, or develop into a typical encephalopathy. Troops stationed in malarial regions receive mepacrine in small doses daily, the effect of which is to produce a state of passive immunity to malaria—the so-called suppressive treatment—while men repatriated from a malarial theatre of operations are given a routine course of the drug on return home as a prophylactic measure. In the great majority of cases, no ill-effects are observed beyond yellow staining of the skin, but occasionally in subjects with an idiosyncrasy to the drug the results may be disastrous, and some of the most malignant forms of dysglycia may be precipitated in this way. Generally speaking, it may be stated that mepacrine should never be used for a case in which there is any suspicion of emotional instability or family history of mental disorder, quinine or plasmochin being advisable instead.

Among physical agents, head-injuries undoubtedly play a part in some cases. The encephalopathy may come on within a few days or weeks of the injury, and is usually of the dysglycic type (*See case* 32). It may or may not be associated with memory-defects and other signs of the post-traumatic syndrome. Peripheral injuries, such as fractures, may also precipitate encephalopathy in certain cases; case 25 is an example of this.

Heat and exposure to stress under tropical and sub-tropical conditions are undoubtedly exciting causes in some acute and subacute cases. It is not infrequently found that men with a previously stable personality and good home-service record break down for the first time when exposed to tropical conditions. This kind of history is not at all uncommon in patients invalided from the Middle East and South-East Asiatic regions. In the opinion of the writer, the importance of these climatic and toxic factors

has not received sufficient recognition in the literature, whereas excessive emphasis has been laid on constitutional liability to mental breakdown. Undoubtedly, many who break down under conditions of overseas service frequently have a previous neuropathic history, but their numbers are equalled by those whose pre-encephalopathic history and service-record are good and indicative of a stable personality, yet who develop an acute breakdown as soon as they are exposed to conditions of stress in the front line or in tropical regions. The writer is therefore of the opinion that in all assessments of attributability to military service, the history of breakdown under such conditions cannot be ignored.

In those cases where the breakdown occurs as the result of heat-exhaustion, the symptoms have a sudden onset as an acute delirium with excitement and mental confusion, the subsequent evolution of which is to a typical dysoxic confusion or dysglycic excitement. In other cases, the onset may be insidious, with a history of the gradual development over a period of several weeks or months of abnormal fatigue, apathy, depression, and conduct-deterioration. Later, sensory features in the form of hallucinations and delusions make their appearance, the eventual clinical picture being a typical malignant or paranoid dysoxia.

Psychological causes may be divided into those operating under home-service and those under overseas service conditions. Of the former, the most important are ; enforced and prolonged separation from home ; domestic troubles, especially marital infidelity ; and loneliness and monotony due to prolonged spells of duty in isolated and remote regions, where facilities for recreation and contact with civilization are few or non-existent. In some more intelligent but emotionally unstable types, an acute manic type of reaction may suddenly occur following promotion to a position of responsibility or attainment of a commission. The endogenous forms of encephalopathy have in general as causal factors the same kinds of mental conflicts and stresses as are found in civil practice.

In overseas theatres, exposure to battle-stress is an important cause of breakdown. Of immediately precipitating conditions, the most important are exposure to blast from explosions, heavy bombing, prolonged lack of sleep due to continuous action in the front-line, and terrifying experiences, such as being trapped in a burning tank, or seeing a friend killed in action. In these cases, the encephalopathy usually starts as an acute confusional or panic

reaction, or as an acute autonomic upset, with the somatic signs of intense anxiety.

In repatriated prisoners of war, the common cause of encephalopathy are prolonged confinement and boredom, malnutrition and long forced marches in severe weather. The catatonic and depressive paranoid forms of dysoxia are the most common types found, and the derealization type of reaction is not uncommon. Not infrequently it is found that the encephalopathy only develops after repatriation. Delusions of persecution are a very common feature of encephalopathy in prisoner-of-war cases.

(3) Constitution and Personality.

As in civilian practice, certain definite personality types are found in association with the different forms of metabolic reaction. Thus, mental deficiency in its milder forms is not uncommonly found associated with the dysoxic syndrome. In dull and backward men who develop an acute metabolic breakdown under service-conditions, acute dysoxia appears to be the commonest type of reaction. The influence of mental defect on the course and prognosis will be referred to in a later section of this work.

The rigid, over-scrupulous, and obsessional type of personality is especially liable to develop the benign affective and derealization forms of dysoxic reaction. In these cases, the usual precipitating factors are duties involving an excessive degree of responsibility, with subsequent worrying and anxiety. Aggressive, suspicious, and contentious personalities who break down usually develop the paranoid or manic form of dysoxia or dysglycia. The timid, inadequate and solitary type, which is lacking in stamina and toughness, usually develops the paranoid-depressive type of dysoxia. The malignant form of dysglycia is commonly seen in the introverted and typically schizoid individual, but it also occurs not uncommonly in the cheerful, over-active, and extraverted type, especially when under conditions of stress, overwork, and responsibility, or of climatic stress in tropical theatres. Some of the most malignant and fulminating types of dysglycic reaction are seen in these cases.

A large proportion of acute depressive dysoxic states, generally with a good prognosis are seen in Air Force personnel, who have been stationed for long periods in isolated and lonely places while on home-service.

Before leaving the question of ætiological factors, reference should be made to the subject of deficiency-diseases and avitamin-

osis in relation to metabolic encephalopathy. It is the writer's view that vitamin deficiency has no place in the ætiology of this group of diseases. In the series of cases studied, none was encountered which presented any evidence of vitamin deficiency, or which benefitted in any way from the exhibition of vitamin preparations, while at the same time failing to respond to the standard methods of neurometabolic therapy.

The type of case which would be expected to show the features of avitaminosis is that of liberated prisoners of war, who have been kept for several years in an enemy prison camp under conditions of chronic malnutrition. The author has handled many of these cases and the commonest form of reaction found is an acute catatonic dysoxia or dysclycic excitement of the ordinary type described in this work. These cases have the same clinical features, course, and response to neurometabolic therapy as the ordinary type, do not present any symptoms suggestive of avitaminosis, and are not benefitted by vitamin medication. It would appear from this that the role of the vitamin complexes in cerebral oxygen-glucose metabolism and its disorders is a secondary one, and that it is possible for normal cerebral function to be compatible for long periods with a severe degree of vitamin-deficiency.

(4) Attributability to Military Service.

One of the most controversial questions regarding the metabolic encephalopathies which occur under military conditions has been that of their attributability or otherwise to military service. It is generally held at the present time that the typical encephalopathies are due to constitutional factors and not to the stresses of military conditions, and that men who exhibit this form of mental breakdown under service-conditions would in any case have broken down sooner or later under the conditions of civilian life. The argument usually advanced in support of this contention is that, in a large proportion of such cases, there is evidence of constitutional nervous instability in the form of a family history of psychopathy or evidence of previous instability in the patient.

From a consideration of the facts set forth in this chapter three fmportant points will be evident. Firstly, there is no evidence for supposing that metabolic encephalopathy cannot be induced by the exogenous stresses described above ; secondly,

this form of cerebral disorder does in fact occur in a large number of cases as the direct result of such stresses; and thirdly, in a substantial proportion of such cases there is no evidence whatever to suggest that the patient was constitutionally predisposed, the family history and previous personality being well within the limits of normality.

The conclusions drawn by the writer therefore are as follows :—

(1) Cases of metabolic brain disease occurring in men of good previous personality under conditions of stress while serving overseas should be considered as wholly attributable to military service.

(2) Cases occurring under similar conditions in men with a definite pre-encephalopathic or family history of nervous instability should be considered as materially aggravated by military service.

(3) Cases occurring under home service conditions, with or without a previous neuropathic history, and where there is no evidence of special stress, cannot be considered as caused or aggravated by conditions of military service.

CHAPTER IV

CLASSIFICATION AND TERMINOLOGY

Few psychiatrists will dispute the statement that the most difficult and unsatisfactory aspect of psychiatry as a whole has been the absence of a satisfactory terminology and ætiological classification of the conditions described. General medicine and surgery for the most part make use of terms which are pathologically and anatomically descriptive; psychiatry, on the other hand, has never up to the present time been based on a known pathology and has had to content itself with a terminology descriptive of symptoms only. Examples of such terminologies are the Kraepelinian, which is ætiological only in respect of the organic types; the terminology of Bleuler, which is hardly any better, and Adolf Meyer's classification by reaction types (ergasias), which, again, is purely symptomatological.

The number and variety of classifications which have been proposed up to the present time is in itself a striking testimony to their unsatisfactory nature. The net result up to now has been the production of a variety of pretentious Greek terms, but not the attainment of any understanding of the true nature of the conditions described. The classification proposed by the writer in place of those in use at the present time has the advantage of being much simpler, uses a minimum of composite Greek terms, and is ætiological instead of being merely descriptive of symptoms. It is based on the hypothesis of disordered cerebral oxygen-glucose metabolism, and the specific response of the various mental syndromes to the anoxic and hypoglycæmic therapies, as observed in a series of several hundred cases of recent encephalopathy treated by the writer.

As the result of these observations, three outstanding new facts have become evident regarding the nature and causation of these conditions. First, that all the symptoms and signs, as well as the response to specific treatment, can be explained on the basis of the metabolic hypothesis; second, that two distinct types of metabolic encephalopathy can be distinguished according to their response to anoxia and hypoglycæmia; and thirdly each of these two main types can be differentiated by a distinct syndrome of clinical symptoms.

In the classification proposed by the writer, the term "metabolic encephalopathy," or simply "encephalopathy" is employed to denote all the conditions of cerebral disease under consideration, the expression "psychosis"—i.e., a disorder of the psyche—being dropped altogether, and the term "encephalopathy"—i.e., a disease of the brain used in its place. This is, of course, analogous with the terminology used in general medicine for cerebral disorders due to organic causes, examples of which are "hypertensive encephalopathy" for the cerebral disturbance found in hyperpiesis, and "arsenical encephalopathy" for that found in arsenical poisoning. The term "metabolic encephalopathy" also serves to distinguish the conditions which it includes from the organic reaction-types, which in this classification are grouped under the general term of "organic encephalopathy."

Two main forms of metabolic encephalopathy can be distinguished. The first type is refractory to hypoglycæmic but responds to anoxic, therapy, and for it is proposed the term "dysoxic encephalopathy," or "dysoxia"—that is to say, a disorder of the oxidation-processes of the cerebral tissue. The second type is refractory to anoxic, but responds to hypoglycæmic, therapy, and for it is proposed the term "dysglycic encephalopathy" or "dysglycia," signifying a metabolic disorder involving the glycolysing processes of the brain-tissues.

The dysoxic form is approximately equivalent to the affective disorders in the orthodox terminology, and exhibits as its characteristic features the following symptoms; dysphoria, apathy, retardation, hypokinesia with katatonic features, bradyphrenia and ideational poverty; apprehension, agitation and unpleasant mental tension, with confusion, perplexity, and disorientation; and delusions and hallucinosis of the nociphronic type, with a strongly appropriate emotional reaction.

Dysoxic encephalopathy therefore includes the following clinical conditions:—

1. The endogenous depressions, depressive stupors, involutional melancholias and certain forms of mania of the tense, querulous and agitated type.
2. The simple form of schizophrenia, including the apathetic form and the confusional and katatonic stuporose types.
3. Certain forms of depressive state associated with derealization and depersonalization-symptoms.
4. Certain forms of obsessive-ruminative conditions associated with a depressive emotional reaction.

5. Paranoid states with an emotional setting of depression and apprehension, with unpleasant hallucinations; some forms of alcoholic and drug-encephalopathy are included in this group.

6. Delirious and post-infective exhaustion states characterized by stupor and depression.

Anoxic therapy is specific for the dysoxic group of disorders. It appears to have a primarily stimulating effect on the cerebral oxidation-mechanisms, which are at fault in dysoxia. The characteristic dysoxic symptoms of apathy and retardation are always completely refractory to hypoglycæmia.

The dysglycic form of encephalopathy is equivalent to the classical schizophrenic and delusional reaction-types. Clinically, the symptoms which distinguish it are the opposite of those of dysoxia, and are as follows; elation, euphoria, excitement, flight of ideas, general acceleration of the stream of thought, over-activity, and hyperkinesia; a peculiar and characteristic disorder of thinking and association, seen typically in the malignant form of dysglycia (hebephrenia in the orthodox terminology); emotional incongruity, fatuousness, a bizarre affective response, and a wealth of bizarre delusions and hallucinations. Disorientation may be present in the very acute forms, but the characteristic apathy and depression of dysoxia are not found, except as secondary symptoms in some cases.

Dysglycic encephalopathy therefore includes the following clinical conditions:—

1. Simple mania and hypomania.
2. Hebephrenic schizophrenia of the classical type.
3. The delusional states, both systematized and non-systematized, that is to say, the conditions known in the orthodox terminology as dementia paranoides, paraphrenia, and paranoia.
4. Certain delirious states, alcoholic and drug-encephalopathies, in which the symptomatology is predominantly of the type described above.

This form of metabolic disease is entirely resistant to anoxic therapy, but responsive to hypoglycæmia, which appears to have a specific effect on the disordered glycolytic processes and the characteristic thought-disturbance produced thereby, together with a specifically tranquillizing effect upon the excitement and morbidly accelerated cerebration.

It will be evident from this description that the dysoxic form of reaction is, from the psychopathological point of view primarily a disorder of the affective mechanisms, the delusional and hallu-

cinatory features being secondary symptoms; whereas, on the other hand, the dysglycic form is primarily a disorder of the sensorium and the mechanisms of association and interpretation. In anatomical and physiological terms, we might say that in dysoxia the thalamic centres with their connections are the regions principally selected for attack by the morbid process, while in dysglycia it is the sensory-psychic and association areas of the cortex which are primarily affected. Thus, to take some of the more prominent mental symptoms as examples; the simple and katatonic-depressive forms of dysoxia would, on this hypothesis, be regarded as affections of the oxidizing functions of the thalamic centres, fronto-thalamic association neurons and tracts, and their cortical connections; simple mania of the anoxia-resistant type would be regarded as a disorder of the glycolyzing functions of the same regions; hebephrenia of the insulin-sensitive type would be the same, with the addition of a diffuse dysglycic lesion in the cortical sensory and association systems; the delusional encephalopathies of later life are primarily dysglycic disorders affecting the cortical regions concerned with the reception and interpretation of sensory impressions judgment, and discrimination; while the predominantly hallucinatory states would be dysglycic upsets of the cells of the visuo-sensory and acoustico-sensory areas and their association-tracts.

An important feature of this classification should be emphasized at this stage. This is the fact that, although the symptomatology in a given case is important as an indication of which of the two classes it should be assigned, the all-important deciding factor is the response to anoxic and hypoglycæmic therapy. This response is the only absolute and reliable criterion, since certain symptoms are common to both types of metabolic disease, and forms which are typical in symptomatology are not uncommonly encountered. (See Ch. VII, p. 87.)

The importance of the clinical differentiation of the dysoxic and dysglycic syndromes from the therapeutic point of view will at once become apparent from a consideration of these facts. The differential diagnosis, with its difficulties and practical applications, will be fully discussed in a later chapter.

It should be emphasized at this point that the dysoxic and dysglycic syndromes should not be regarded as distinct and mutually exclusive conditions. It is obvious that cerebral

oxidation and glycolysis are closely connected and interdependent processes, and that an upset of one process will naturally have profound repercussions on the other. Also, it is known that oxidation-processes are directly influenced in hypoglycæmia, and glycolytic processes in anoxia; thus, it would probably be more accurate to consider both disorders to be the same basic condition, with, in dysoxia principally dysoxic, and in dysglycia principally dysglycic, mechanisms underlying the symptoms.

Combined and alternating forms can certainly be distinguished, obvious examples of which would be the phases of mania and melancholia in the affective types of disorder, and the alternating phases of stupor and excitement in the katatonic types. In this type of case, it would be probably more accurate to speak of the dysoxic phase, or the dysglycic phase, rather than to classify them rigidly under one or other of the two main types.

It will be evident to those readers accustomed to the orthodox psychiatric conceptions and terminology that the classification just described presents several novel and completely unorthodox features. In the first place, a completely new conception of the nature and mechanism of this group of disorders is introduced —the concept of them as physical diseases with an organic pathology rather than simply as disorders of mental function. Secondly, the old system of a large number of symptomatological terms for the different clinical symptom-groups is entirely dispensed with, all the aforesaid conditions being divided into two simple classes—the dysoxias and dysglycias. The advantages of this greatly simplified system of classification will at once be obvious.

Thirdly, certain symptom-complexes usually regarded as one disorder in the present-day terminologies are divided into separate diseases in the metabolic classification. Thus, for example, the conditions grouped under the term "schizophrenia" in the orthodox classification are divided into two distinct categories, the dysoxic and dysglycic forms. Similarly, the syndromes of mania and melancholia, hitherto grouped together as the manic-depressive psychosis, are separated, mania falling into the dysglycic and melancholia into the dysoxic class.

Fourthly, two other conditions, namely obsessive—ruminative and depersonalization states, are included in the group of dysoxic disorders; up to now, these conditions have always been included in the psychoneurotic group of mental disorders.

Finally, the nomenclature employed is greatly simplified in comparison with that of the orthodox terminologies. It involves

the use of only two new Greek words—" dysoxia " and " dysglycia "—and the borrowing of a third—" encephalopathy "—from the terminology of general medicine. The use of words such as " psychosis," " insanity," " schizophrenia " and so on, with all their sinister associations, is thus discarded altogether.

There is, however, one practical difficulty in the adoption of this form of classification, which will be at once apparent to the psychiatrist who is familiar only with the type of encephalopathic patient commonly encountered in civil mental hospital practice. This is the comparative rarity in civil practice of the acute and typical dysoxic and dysglycic clinical pictures seen so commonly under military conditions. In civil life, the general run of cases are of a much more chronic type, in which the original clinical features have become blurred and distorted in the course of time by such secondary features as cerebral deterioration and dementia. It is thus often very difficult to say whether a particular patient was originally a dysoxic or a dysglycic case at the time of onset of the original metabolic breakdown. Moreover, in such chronic cases, the response to neurometabolic therapy may be of little help as a diagnostic test, since the longer the duration of the disease, the poorer the response to treatment, which in cases of more than a year's duration may be practically nil—at any rate in the case of the malignant dysoxic and dysglycic forms.

It should therefore be borne in mind that the typical dysglycic and dysoxic features can often only be distinguished in the early stages of the disorder, before irreversible changes in the brain-tissues have set in. In the terminal and quiescent phase of the disorder, where any great degree of neuronal degeneration has occurred, the usual end-product is a quiet, apathetic, and demented patient, in which it may be difficult or impossible to tell whether the original attack was dysoxic or dysglycic in type. These remarks apply especially to cases of the malignant forms of both disorders, which tend generally to produce rapid and progressive mental deterioration; in conditions such as the depressive and involutional dysoxias, however, which may last for many years without evidence of deterioration, the anoxic response is generally always good, so that the foregoing remarks do not apply to these cases.

It will thus be evident that the typical dysoxic-dysglycic syndrome is rarely seen in the pure form in civilian as compared with military practice, and that consequently a considerably more prolonged and painstaking scrutiny may be required before

it is possible to definitely assign any given case of long duration to either of the two groups of metabolic disorders.

The proposed classification of the metabolic brain-diseases is set out in schematic form at the end of this book.

CHAPTER V

THE DYSOXIC ENCEPHALOPATHIES

Dysoxic Brain-Disease

The dysoxic form of encephalopathy is the commonest type of metabolic brain-disorder encountered in military practice, accounting for at least three-quarters of the total number of encephalopathic patients admitted to hospital and diagnosed as such. It may be defined as a primary metabolic disorder of the brain, in which the functions of the oxidizing cells of the higher centres are principally affected, and which responds favourably to anoxic therapy. Its cardinal features are clouding of consciousness, slowing of cerebration, mental tension and depression, nociphronic hallucinosis principally in the auditory sphere, and ideational disorder in the form of persecutory delusions and ideas of death.

Although a mixed symptomatology is frequently encountered, the following four principal types may be distinguished :—

(1) The malignant or relapsing type, which in military practice is by far the most common. This includes, in the orthodox terminology, the simple type of schizophrenia, characterized by apathy, emotional blunting, progressive withdrawal from reality, and an early age of onset, and the katatonic or depressive-confusional types, associated with ideas of death, guilt, and self-reproach, periods of stupor and recurrent episodes of mental confusion.

(2) The benign, or affective type, corresponding to the manic-depressive and involutional melancholia of the orthodox nomenclature. This form, in contrast to (1), shows little tendency to mental deterioration.

(3) The paranoid type, in which the principal features are delusions and hallucinosis of the nociphronic variety in a setting of depression and relatively clear consciousness. Two subdivisions of this form can be distinguished—the quiet, apathetic and depressed form, and the agitated form, in which the emotional reaction is one of severe tension, apprehension, and fear, associated with intensely unpleasant hallucinations in the auditory sphere.

(4) Certain types of obsessional state, with persistent autochthonous thoughts and ideas, which are accompanied by a strongly appropriate dysphoric affective reaction, and respond favourably to electro-anoxia. The derealization-depersonalization syndrome may conveniently be included in this group.

The ætiology and common precipitating factors have already been indicated. Several characteristic modes of onset, which may be acute or insidious, are commonly found.

The disease may commence suddenly as an acute confusional amnesic state or stupor. Thus, an acute stupor with mutism and negativism, and with or without katatonic features, may suddenly manifest itself and may in the first few days be mistaken for an acute hysterical fugue state. Peculiar behaviour, signs of toxæmia, and faulty habits are commonly found in the more acute forms. More commonly, after a few days or weeks of increasing loss of efficiency and depression, a dull disorientated amnesic state may gradually manifest itself. This is a common mode of onset in the confusional-catatonic forms.

In other cases, an acute depressive episode, with severe emotional upset, tension, agitation, restlessness and fear may be the first sign of the commencing encephalopathy. In this form an impulsive suicidal attempt coming suddenly out of the blue in a previously normal and apparently stable personality may be the first manifestation. Such suicidal attempts are often apparently causeless and impulsive, and in military practice may take the form of self-wounding by shooting with a rifle, slashing the wrists or throat with a razor blade or less commonly, poisoning by aspirin, disinfectant, or other easily-obtained noxious agent. In this type, the prodromal symptoms are often those of acute distress, tension, and anxiety, and may often lead to the diagnosis of an acute hysterical or anxiety-state.

In the simple form, a gradual and insidious personality-change is characteristically observed. Thus, for example, a man who has previously been a keen and efficient soldier may be noticed, often by his N.C.O.'s or officers, to be gradually becoming slovenly, careless, and inefficient, with a marked loss of interest and initiative. Repeated petty infractions of discipline are common, such as absence without leave, drunkenness, insubordination with causeless temper-tantrums, and impulsive outbursts which frequently lead to assaults on N.C.O.'s and officers. This history of sudden personality-change in a previously good

soldier is alone often absolutely diagnostic of the condition, and these cases are frequently brought before the psychiatrist in the first place as disciplinary problems. In other cases, where the disease has been of very insidious onset and evolution, the man may have been noted from the beginning to be unable to grasp his elementary training, slovenly and careless in habits, generally useless as a soldier, and a continual liability to his unit. Such men are often tried in various duties without success, descending finally to sanitary orderly or unskilled cookhouse-assistant until at last they are consigned in despair by an exasperated commanding-officer to the psychiatrist. It is in this type of case that the diagnosis from mental defect is often difficult, and the true nature of the condition can only be ascertained by careful and prolonged observation. It is often found in these cases that the disease has been present for a considerable period prior to joining the service, the symptoms on joining having been so slight as to pass undetected by the medical recruiting-board.

Acute excited states with delirium and conduct and language-peculiarities, are less commonly found as initial symptoms in dysoxia, being much more characteristic of the dysglycic form of encephalopathy.

The last and not least important mode of onset in dysoxia may be with symptoms simulating a simple anxiety state or acute emotional upset. The patient may first report sick complaining of headache, loss of concentration, mild depression with feelings of tension, and " blackouts " or phases of mild confusion—the four commonest symptoms of anxiety-state. Typical dysoxic symptoms such as hallucinosis and ideas of reference are often absent at first, and only become manifest after a considerable period of observation. Alternatively, a dysoxic illness may come on acutely in the guise of a simple emotional crisis ; in such cases, there is not uncommonly an apparently obvious precipitating cause, such as the death of a relative or marital infidelity, and the patient may pass suddenly into an acutely depressed, tearful, and agitated state. This, at first an apparently typical reactive depression, soon reveals its true nature when it fails to clear up, and mental confusion, hallucinosis, and other characteristically dysoxic signs gradually make their appearance. A sudden suicidal attempt at the onset is a common feature in these cases.

Clinical Features

The account which follows is based on prolonged observation of the cardinal encephalopathic symptoms as presented in a series of several hundred military psychiatric casualties. A detailed description and analysis of the psychopathological aspects will not be attempted since this does not differ essentially from that found in civilian cases, and full descriptions can be obtained from any of the standard text-books on mental disorders. Instead, the most important aspects of the symptomatology with regard to the differentiation of the dysoxic and dysglycic syndromes will be discussed, and illustrated by records of actual cases studied by the writer.

In dysoxia, the symptoms may be conveniently considered as falling under those of thought, affectivity, the sensorium, ideation, and motor and habit disorders. A general account of the various symptoms will first be given, followed by a brief clinical description of the four main types.

The most profound disorders of the stream of thought and its content are found par excellence in the confusional and catatonic forms. Most characteristic is a dazed, perplexed and confused state, with marked retardation and slowing of the cerebral processes, diminution of motor activity, intrapsychic tension, and pronounced depression of mood, which may amount to complete stupor of simple or katatonic type.

The acute confusional dysoxic is dull, perplexed and often profoundly disoriented in time and space. He usually shows a blank, perplexed expression, with a peculiar stare and ironing-out of the facial muscles of expression, the whole effect being singularly reminiscent of what is seen in cases of general paresis or post-encephalitic parkinsonism. He usually lies passively curled up in bed, or may sit up staring vacantly in front of him, restlessly picking at the bedclothes, and appears to be completely detached from his surroundings. Questions are answered slowly and hesitantly, if at all, and in low monosyllables; often the only response to a question is a dazed, blank stare. The disorder of volition may vary from a mild degree of retardation to complete thought-blocking and mutism. Speech, if present, is often rambling and disjointed, with perseveration and echolalia. Judgment and insight are grossly disordered; when questioned about his symptoms, the patient is often completely unable to describe his feelings, or to give any account of himself. Thus, a

profoundly confused and depressed dysoxic may simply state in response to questions that there is nothing the matter with him, or may produce a hopelessly inadequate rationalization, such as " I'm worrying about home," or " I feel a bit run down." This characteristic inability of the patient to describe his feelings is the most usual form of dyssymbole found in dysoxic disease.

Delusions of a fleeting and ill-defined nature are frequently found in the confusional-katatonic forms of dysoxia. They are nearly always of persecutory or self-reproachful content. Ideas of unworthiness, inadequacy, and self-reproach are common, such as the following ; he feels that he has been a disgrace to the army, has ruined his comrades, or his people at home, he is unclean. has contracted venereal disease, has been a failure, and ought to be killed. He may say that he is talked about, pointed out as a disgrace, accused of having V.D. by his comrades, and is going to be court-martialled and shot. Ideas of guilt and self-reproach centring round autoerotism and sexual misdemeanours are common.

These delusions are always accompanied by a strongly appropriate emotional reaction of fear, perplexity, and depression ; affective incongruity is not characteristic of dysoxia, at any rate in its early stages. The delusions are largely secondary to the affective reaction, and not to bizarre paræsthesias as in the dysglycic states. They are not nearly so persistent as in the latter condition, and respond rapidly to anoxic therapy. This statement requires to be qualified to a certain extent in the case of the paranoid forms, as will presently be described. In the same way, bizarre paræsthesias, such as feelings of control, influence, electricity, and so on, although they occur in the dysoxic states, never attain the vivid and peculiar quality which is found in dysglycic disease. Visceral sensations, such as feelings of blankness or emptiness in the head, or of dysfunction of the bowels and stomach, are fairly common in dysoxic depressions, as are ideas of poisoning, drugging, or persecution by poison-gas or fumes.

In many katatonic dysoxics, complete ideational poverty and blankness are found ; in these cases, usually of the most malignant type, the condition simply takes the form of a dull, confused, perplexed state, in which hallucinations, delusions, feelings of passivity and other positive symptoms of cerebral dysoxia are completely absent.

Of sensory disorders, the visceral and cephalic paræsthesias

of simple type have already been described. Hallucinosis of the complex type is almost always in the auditory sphere. The commonest form is that of threatening, persecutory, or reproaching voices, which may be of the intracampine or the extracampine type. A not uncommon form is that of the voice of the patient's wife, child, or someone else closely attached to him ; this form appears to be particularly common in patients of low intelligence. The hallucinations, like the delusions, frequently centre round such topics as autoerotism and sexual misdemeanours, and these last are especially common in the katatonic forms. As with the delusions, they are accompanied by a strongly appropriate emotional reaction.

In the visual sphere, illusions of misinterpretation are the most common symptom, true visual hallucinosis being rare in dysoxia. The patient may complain that he feels " there is something funny going on all around him," or that other people point at him, make signs and derogatory remarks, read his mind, influence and control his actions, and otherwise persecute and interfere with him. These illusions are commonly connected with the patient's delusions of guilt, uncleanness, and ideas of bodily disease, and are most characteristic of the hallucinatory-paranoid forms.

The characteristic affective disorder in the malignant types is the dull, perplexed, depressed state already described. In the simple affective type, the characteristic melancholic reaction is the rule, with either a state of quiet retarded, hopeless depression, or an acutely agitated and apprehensive reaction. In the simple apathetic form of malignant dysoxia a general emotional dulling and flattening with apathy, detachment from reality, and partial or complete loss of the normal affective responses is the rule. In the hallucinatory-paranoid forms, querulousness, suspicion, rage, and outbursts of aggressive excitement in response to the intensely disagreeable hallucinations is often found. In the manic form of dysoxia, the patient is often querulous, irritable, and agressive ; in spite of the apparent euphoria and exhilaration, there is evidence of a very strong degree of internal psychic tension, which indicates that the condition is a true dysoxic reaction.

To sum up, the characteristic affective disorder, in the form of depression and retardation, confusion and perplexity, agitation and tension, or apathy and loss of interest, in association with delusions and hallucinations of the nociphronic type, may be

regarded as the hallmark of the dysoxic group of brain-diseases, and the principal diagnostic sign of these conditions.

Disorders of the motor functions at the highest level are seen in their most bizarre and characteristic form in the katatonic type of malignant dysoxia. The classical plastic rigidity, flexibilitas cerea, peculiar attitudes and grimaces, with stupor, negativism, and refusal of food are seen at their best in this form of metabolic disease. In the simple and confusional form where katatonic signs are absent, a general diminution of spontaneous psychomotor activity, which may amount to complete stupor and inaccessibility, is usual. Restlessness and purposeless activity is common, and the patients when left alone often tend to wander about the ward in an aimless and perplexed manner. Refusal of food, incontinence, and dirty habits are usual in the more severe forms, but autoerotism, destructiveness and maniacal violence are much less commonly found than in malignant dysglycia. In the simple form, general anergia and loss of normal motor activities secondary to the apathy and withdrawal from reality are the general rule.

In the hallucinatory-paranoid type, aggressive outbursts and impulsive attempts at suicide while under the influence of persecutory hallucinations are often found, as are also sudden attacks on other patients or attendants in the ward. The suicidal attempts are particularly liable to occur in patients with persistent and extremely distressing aural hallucinosis, and it has been the author's practice always to regard such cases as actively suicidal, even in the absence of a history of suicidal attempts or other definite evidence of suicidal tendencies.

The intellectual disturbances found in dysoxic states merit especial mention. It is commonly stated in most leading text-books, even at the present day, that in " schizophrenia "—that is to say, in malignant dysoxia—true intellectual impairment with clouding of consciousness is rare. This statement has, in the writer's experience, been found to be absolutely untrue in the acute forms, and it is time it disappeared from psychiatric text-books. In the malignant form, as already indicated, gross disorientation in time and space, with impairment of memory and comprehension of organic type is the rule rather than the exception. It is also not uncommonly found in the simple form of dysoxia, and frequently in the acute dysglycic states. It can be readily demonstrated that this memory-disorder is a true intellectual disturbance, and not simply an apparent disorder

due to apathy and indifference, by the application of simple intellectual tests. In early cases, it is a temporary phenomenon, but in those which deteriorate it often becomes permanent and irreversible. Dysoxia of the malignant type and the malignant form of dysglycia (hebephrenia) are especially prone to produce permanent dementia, and the importance of this and the therapeutic problems raised thereby will be fully discussed in the sections on Prognosis and Treatment.

In acute dysoxia, memory for recent events is principally affected, that for remote events to a smaller extent. In the most acute confusional forms, the patient is profoundly disoriented in time and space, and is unable to remember dates, names, or anything of his past history; as in other types of delirious states, comprehension is gravely impaired, and he may be completely unable to find his way about the ward, and often mistakes identities, imagining that other people in the ward are his relatives or parents. Confabulation is occasionally seen, and a massive circumscribed amnesia is not uncommon; this last feature may persist after recovery from the acute episode has been otherwise complete.

Another noteworthy feature of the memory impairment is that, contrary to what has been asserted by a number of writers, it is not made worse as the result of anoxic therapy, but is actually one of the first symptoms to show improvement with this form of treatment. This point will be mentioned again in a later chapter, when the question of neurometabolic therapy and its effects is discussed in detail.

In some cases of the simple type, however, the extreme apathy, indifference, and lack of concentration may produce a spurious appearance of intellectual deterioration; but, on intellectual testing, the powers of remote and recent memory are found to be surprisingly intact, considering the degree of affective and volitional disorder present.

The vegetative disturbances of acute dysoxia include persistent and severe insomnia, constipation, anorexia, and the general signs of an acute toxæmic state. In the most acute forms, cachexia and emaciation may occur early in the disease and may rapidly become extreme. Circulatory disturbances such as acrocyanosis are not commonly observed and are more commonly characteristic of the chronic and deteriorated type of patient seen in civilian institutions.

DESCRIPTION OF THE FOUR MAIN CLINICAL TYPES.

(1) The katatonic-confusional or malignant type

The principal clinical features of this type have already been described. It is by far the commonest form of acute dysoxia occurring in military practice, in which it is seen in its most fulminating and rapidly dementing form. It occurs characteristically in the younger age-group, the incidence being in the group 18 to 25 years. It may rightly be termed "malignant," for when untreated it has a marked tendency to progress to general physical and mental deterioration with severe terminal dementia. The progress of the disease may be extremely rapid and the patient may in the course of a few weeks or months become progressively more dull and apathetic, wet, dirty in habits, and demented, with progressive destruction of the higher intellectual faculties. The course of the disease may be continuous and relentless, or the patient may make temporary rallies to comparative lucidity, only to relapse again and again into a confused, dull, and apathetic state. In the most severe cases, the degree of final emaciation and cachexia may be extreme, the end-state being death by intercurrent infection.

Its most striking features are the profoundly confused, dull and perplexed state, and the markedly depressive affective reaction. Characteristic is the tendency to repeated attacks of confusion, with more or less lucid intervals of remission. It responds dramatically to electroanoxia, but is completely resistant to hypoglycæmia. Of all the dysoxic encephalopathies, this form shows the strongest tendency to repeated relapses.

The katatonic form is distinguished by the addition of the peculiar motor signs, which are probably due to the dysoxic process selecting the frontal lobe-neurons and their premotor connections for the brunt of its attack. The katatonic phenomena are in no way different from those found in such cases in civilian practice. This form is on the whole much less common than the simple confusional form and the course, prognosis, and response to electroanoxia are similar. Delusions of self-reproach centring round autœrotism and sexual topics are especially associated with the katatonic form of malignant dysoxia.

The following cases are typical examples of this form of metabolic disease :—

Case 1. This patient was a signalman aged 26. He was invalided from the Middle East, with a history of acute

confusional breakdown of insidious and progressive onset, and marked by the exhibition of peculiar and bizarre conduct. On admission, he was dull, confused, very retarded, vacant in expression, difficult with food, and required strong sedatives at night owing to restlessness. He exhibited the dazed, perplexed and profoundly disoriented condition just described, with very marked thought-blocking and complete inability to express his feelings intelligibly or to describe his symptoms. Oral hallucinations of persecutory type were present. Physical examination was negative.

He responded dramatically to electroanoxia, complete abolition of the dysoxic symptoms being attained after seven applications. After a week or so of normality however, he relapsed again just as dramatically into the acute dysoxic state. He received a total of four courses of electroanoxia totalling altogether twenty convulsions, with final recovery, and was discharged to his home in remission. When last heard of, he was keeping well and working regularly.

Case 2. The patient was a sapper aged 21. He was invalided from the Italian front, with a history of sudden onset of an acute depressive-confusional breakdown following exposure to heavy shelling. On admission, he was dull, mute, stuporose and retarded, completely apathetic and inaccessible. He showed evidence of oral hallucinations of persecutory type with marked ideas of guilt and self-reproach ; when not completely stuporose, he was rambling and disjointed in speech. Katatonic signs were absent, and physical examination negative. A mild degree of feeble-mindedness was evident. He responded in the usual dramatic manner to electroanoxia, only to relapse repeatedly. He received altogether three courses of treatment, and when discharged to the care of his relatives was in a state of social remission ; residual symptoms were present in the form of a mild degree of dullness, lack of initiative, and emotional instability.

The above two cases are typical examples of malignant dysoxia. The dull, confused and perplexed state, with retardation and anergia, persecutory hallucinations, and good response to electroanoxia with repeated confusional relapses are absolutely typical. These two cases show also how perseverance and energetic therapy can produce a favourable outcome even in this most ominous form of brain disease.

Case 3. This patient, an able seaman, aged 21, was

admitted with a six months' history of oral hallucinations and disordered conduct. On admission he was mute and stuporose, with marked rigidity and flexibilitas cerea, bizarre mannerisms and attitudes, faulty habits, and oral hallucinations of self-accusatory type. These, together with a variety of bizarre delusions of bodily disease and religion, centred round powerful guilt-feelings over past autoerotic activities. Physical findings were negative. He showed the usual dramatic response to anoxia, and exhibited a complete remission, although lack of insight persisted. After the first relapse, he was tried on insulin therapy, with no improvement at all. A further course of anoxic therapy resulted again in mental improvement. He was finally transferred to a naval hospital before treatment could be completed; although greatly improved he was still hallucinated, rather dull, and mildly retarded when discharged.

This case was typical of malignant dysoxia with katatonic symptoms. The outstanding features were the sexual ideas of guilt, marked degree of motor disorder, and characteristic complete failure to respond to hypoglycæmia, with prompt response to electroanoxia.

(2) The Simple Type of Malignant Dysoxia.

This form is in all respects similar in age-incidence and clinical features to its civilian counterpart, which is usually known in the standard text-books by the name of " schizophrenia simplex " or " dementia præcox."

Its principal features are the slow and insidious onset, with progressive apathy and slumping of initiative and interest, absence of positive features such as hallucinosis and delusions, and the comparatively clear setting of consciousness throughout the course of the disease. Occasional confused phases do, however, occur in some cases of dysoxia maligna simplex, as in the other forms. The simple type is much less common in military practice than the confusional-katatonic form, and like the latter condition tends to favour the youngest age-group, as in civilian practice.

The onset usually takes the form of a gradual loss of interest and efficiency in a man who has previously been a reasonably keen soldier. Repeated disciplinary offences are not uncommonly the first symptom which draws attention to the condition. Owing

to its insidious and very chronic course, the ultimate prognosis is usually much less favourable than in the katatonic-confusional type, and it obeys the dysoxic law of response to anoxia and resistance to hypoglycæmic therapy.

The following case is a fairly typical example :—

Case 4. A private, aged 25, with a long record of service, was invalided from India with a history of five years' duration of gradually increasing loss of interest and efficiency. He had in his case-documents a phenomenally large collection of "crime-sheets," extending over the last five years ; his delinquencies included repeated desertions, striking officers and N.C.O.'s, and practically every other crime listed in the regulations, for which he had served numerous sentences of detention without the slightest effect. During the whole of this period, there had, apparently, never been the slightest suspicion on the part of his unit medical officers that he was not mentally normal. On examination, he was facile, apathetic, detached, and completely lacking in insight and in normal interests and activity ; most of the time he wandered or stood listlessly about the ward, made no spontaneous complaints, and had no idea why he had been sent into hospital. A few fleeting auditory hallucinations and ideas of reference were evident, and he showed occasional mild confusional phases. Physical findings were negative. Electroanoxia produced no appreciable improvement, and he was finally discharged to his home unimproved.

Case 5. An airman, aged 32, was invalided from the Middle East while serving a sentence of two years detention For the last twelve months he had shown evidence of progressive apathy, repeated petty offences, and complete inability to assimilate his training. On admission, he was profoundly apathetic, detached, offhand in manner, and showed complete emotional impoverishment. He was completely unable to co-operate or to give an account of himself, his invariable reply to any question being a shrug and a "Don't know." Restlessness, hallucinosis, and delusions were absent, and he was clean in habits and passively obedient The physical examination was negative. He made a very good response to electroanoxia, and was finally discharged the service in a state of remission.

Two cases of simple dysoxia have been described. In both there was a history of delinquency, insidious personality-

deterioration, apathy and loss of interest in the outside world. In case (4), the poor anoxic response was undoubtedly due to the long duration of the disease and the gross degree of cerebral degeneration present. In case (2) the therapeutic result was unusually favourable for a case of this type.

(3) The Affective Type of Dysoxia.

This is the classical melancholia or manic-depressive psychosis of the orthodox text-book classifications. It also includes the involutional depressive states of later life. It is very rarely met with in military practice, on account of its favouring the later age-group, and is exactly similar in all its main features to its counterpart in civil practice. The response to electroanoxia is invariably excellent, and it differs from the malignant forms in that it does not show the relapsing tendency to nearly such a great extent, and there is no tendency to mental deterioration. A typical example of the depressive form is the following :

CASE 6. A flight-sergeant, aged 41, with twenty years regular service, was admitted in a state of acute depression. He had a history of one previous attack, and was a very conscientious, hard-working, over-anxious type of personality, with an excellent service-record. When first seen, he was acutely depressed, retarded, with ideas of self-reproach about autoerotism, and showed aural hallucinosis of the accusatory type. Mild disorientation and the typical melancholic facial expression were present. Physical findings were negative. Two applications of electroanoxia produced a complete remission, and he was returned to duty at his own request, recovered.

This case shows the typical features of the benign, or affective form of dysoxia. The personality-type of the patient, previous history of a depressive attack with recovery, extremely rapid response to anoxia, and late age of onset are the salient features.

(4) The Paranoid Type of Dysoxia

This form is less common than the malignant type, and includes some forms of drug-encephalopathy, such as chronic alcoholic hallucinosis, cocaine-paranoia, and other toxic-confusional states in which the symptomatology shows dysoxic characteristics. Two varieties of paranoid dysoxia may be distinguished, the agitated form and the simple depressed form.

The former, which favours the higher age-group of 30 years and over, is characterized by the presence of vivid and persistent aural hallucinosis of the nociphronic type in a setting of relatively clear consciousness, and little or no tendency to deterioration. The emotional reaction is one of acute fear, apprehension, and distress, and aggressive outbursts and impulsive suicidal attempts are common. It is in this form of encephalopathy particularly that the patient's conduct is entirely dominated by the hallucinations, which, as a general rule tend to be extracampine in location, continuous, and of equal intensity day and night. These patients are some of the most pitiful sights which can be seen in an acute psychiatric ward.

The type of personality which is expecially liable to develop this form of dysoxic reaction is the aggressive, extroverted diathesis; the over-anxious and obsessional is also liable to exhibit this form of reaction.

The hallucinations and delusions in these cases are often extremely obstinate and difficult to influence with anoxic therapy. They are, like other dysoxic symptoms, completely refractory to hypoglycæmia, and indeed appear in many cases to be actually intensified as the result of exhibition of this treatment. To effect remission, a full course of nine to ten applications of electroanoxia is generally required, and often little or no improvement becomes evident until six to seven applications have been given. The tendency to relapse, however, is on the whole less than in the malignant dysoxias, and the ultimate prognosis is usually good.

The second type of paranoid dysoxia, the simple depressed, resembles the malignant form more closely in its clinical features. In contrast to the agitated dysoxic, the patient's emotional reaction is a quiet, dull, depressed, apathetic state, which shows none of the features of acute tension and agitation just described.

The type of personality which usually exhibits this form of dysoxic reaction is the timid, shut-in, inadequate type, and mental deficiency in its milder forms is not uncommonly associated.

The clinical history and picture are usually as follows. A man of the type described above gradually becomes depressed, solitary, and listless, increasingly withdrawn and detached, and develops ideas of reference and persecution referred to his comrades. In most cases the condition is of gradual and insidious onset, but in others the first symptom may be a sudden attempt

at suicide. On examination, the clinical picture is that of a quiet, apathetic, depressed individual, showing a mild degree of retardation, solitary habits, lack of spontaneous interest and activity, and well-marked aural hallucinosis and ideas of reference. The patient is usually well-behaved and co-operative, and although there may be some degree of mild disorientation and memory-defect, there is never the profound degree of confusional disturbance seen in malignant dysoxia. Ideas of guilt are not so marked as a rule as in the katatonic-confusional form; more prominent are the aural hallucinosis of persecutory type and ideas of persecution and passivity. Of these, delusions of poisoning, persecution by poison-gas, thought-reading, and being watched or followed are quite common. A severe degree of depression with marked apathy but little evidence of psychomotor retardation is characteristic. This form of dysoxia responds very well as a rule to electroanoxia, and, like the other dysoxic disorders is resistant to hypoglycæmia. The tendency to relapse is on the whole, less marked than in the malignant form.

The following cases are typical examples of the paranoid dysoxic syndrome:—

Case 7. A signalman, aged 30, was invalided from the Italian front with active pulmonary tuberculosis of the right upper lobe. Soon after arrival in England, and while under treatment for his lung condition at a general hospital, he developed an acute hallucinatory-paranoid state, the first symptom of which was a determined suicidal attempt by cutting his throat with a razor. When admitted, he was restless, agitated, and apprehensive, completely without insight, and showed vivid and persistent aural hallucinosis of nociphronic type. He complained constantly that everyone was talking about him and accusing him of some dreadful crime, said he felt that there was "something queer going on all around him," and that all the time "dreadful things were going through his head," He was restless, sleepless, completely dominated by his hallucinations, and presented a most pitiable spectacle. Physical examination was negative for signs of active phthisis; there was a large healing incision on the front of the neck, the result of his suicidal attempt, and a blood-count showed moderate microcytic anæmia. A skiagram of the chest revealed a moderate degree of tuberculous infiltration of the right lung, apparently in the quiescent stage. He was apyrexial.

In view of the absence of any signs of spontaneous improvement, and the rapid deterioration in his mental state, insulin therapy was commenced, it being considered inadvisable to use electroanoxia on account of the possibility of reactivating the tuberculous condition. A dosage of 180 units was reached without coma, and with no evidence of mental improvement whatever. As no signs of recrudescence of the lung-infection were evident, he was changed over to electroanoxia; nine applications produced a complete remission of dysoxic symptoms, but the phthisis became active again, with cough and positive sputum. The pulmonary condition and anæmia, however, responded well to general medical measures, and he was finally transferred to a civilian tuberculosis sanitorium for further treatment, maintaining his mental remission at the time of his discharge.

Case 8. A sergeant, aged 34, was invalided from Ceylou with a history of paranoid encephalopathy of recent onset. On admission, he was confused, acutely distressed, restless, and apprehensive, with aural hallucinations and delusions that people around him were all talking about him and saying that he had contracted venereal disease. Soon after admission, he made a determined suicidal attempt by cutting his throat with a razor. The most prominent symptom in this case was the persistent unpleasant auditory hallucinations and their effect upon the patient's conduct. He responded excellently to electroanoxia, only to relapse within a week or so of discontinuing the treatment. A course of insulin produced no benefit whatever, and the hallucinosis appeared, if anything, to become worse as a result. A further course of anoxia produced a fairly good remission, and when discharged to his home he was free of dysoxic symptoms,but was mildly anxious and lacking in confidence. He was reported subsequently to have relapsed again, requiring admission to a civil mental hospital.

These two cases are typical examples of this form of dysoxic disease. The noteworthy features are the age of onset in both cases, the characteristic vivid hallucinosis of nociphronic type in a setting of relatively clear consciousness, the strongly appropriate emotional reaction, suicidal tendencies, and typical dysoxic response to neurometabolic therapy.

The following two cases are typical of the simple depressed type of paranoid dysoxia :—

Case 9. A private, Royal Army Service Corps, was invalided from the B.L.A. with an acute paranoid-depressive breakdown. He had a history of previous neurotic tendencies, was of poor physique, and exhibited the characteristics of a timid, solitary, and inadequate type of personality. On admission, he was depressed, apathetic, suspicious, solitary and mildly retarded with some degree of thought-blocking. He believed that the other men in his unit were acting strangely, talking about him, and were plotting to kill him. Aural hallucinosis of persecutory type was apparent, and apart from his suspicious and evasive attitude, he was co-operative, clean in habits, and well-behaved. Following a course of three anoxic treatments, he became much brighter, lost his ideas of reference and hallucinations, but remained timid and lacking in initiative and self-confidence, and solitary in manner. Within a few days of cessation of treatment, he relapsed into his former condition and refused any further treatment. When discharged, his mental condition was substantially the same as on admission.

Case 10. A driver, Royal Army Service Corps, was invalided from Italy with a history of depression, ideas of reference, and persecutory delusions. When first seen, he was quiet, apathetic, depressed and solitary, and believed he was going to be court-martialled and condemned to death. He showed aural hallucinations, and believed that a gang of Air Force men were shadowing him from hospital to hospital with the intention of killing him. He was started on electroanoxia, but after the first application complained of severe pain in his back, an X-ray examination revealing a compression-fracture of the fifth dorsal vertebra. He was therefore changed over to insulin-therapy ; after a course of twelve comas, he showed some improvement, but the ideas of persecution persisted and insight was very defective. Insulin treatment was accordingly terminated, and he received a further course of six convulsions without untoward effects. The response was prompt, and he was finally discharged to his home in a state of remission. His personality was of the soft, overdependent, inadequate type, with lack of self-reliance and assertiveness.

The three main types of typical dysoxic brain-disease and their clinical features have been described, and their type of response to neurometabolic therapy indicated. The fourth type, which includes the derealization-depersonalization and obsessive-ruminative states, is so atypical in many ways that it is assigned a separate description in the section on differential diagnosis and atypical forms. It should be emphasized also that the above clinical descriptions apply mainly to the pure dysoxic states, and that the mixed and atypical forms are not included ; these will also be discussed under the subject of differential diagnosis.

To recapitulate briefly the main distinguishing signs and symptoms of the dysoxic state, therefore, the following may be considered as the hallmarks of this type of metabolic brain-disease :—

(1) Mental confusion and disorientation.
(2) Retardation and perplexity.
(3) Affective disorder of depressive type, with either apathy and dullness, or unpleasant tension and agitation.
(4) Hallucinosis of persecutory or nociphronic type.
(5) Delusions of unpleasant content, such as persecution or ideas of guilt.

CHAPTER VI

THE DYSGLYCIC ENCEPHALOPATHIES

Dysglycia cerebralis may be defined as a disturbance of the glycolysing mechanisms of the brain-cells characterized by pathological changes in the sensory, association, and personality. spheres, and which responds to hypoglycæmic but not to anoxic therapy. As in the case of the dysoxias, the neuronic changes which it produces may be reversible and so curable in the early stages, but if untreated, the condition in the great majority of cases tends to progress to cerebral degeneration and dementia.

The dysglycic form of brain-disease is considerably less common in military practice than the dysoxic type ; this is because a large proportion of dysglycic cases are of the progressive delusional type of later life, the age-incidence of which is rather later than the usual military age. The ætiological and precipitating factors are the same as for the dysoxic states, and have already been discussed. The acute forms especially seem to be liable to be precipitated as the result of prolonged psychological stress, and exposure to severe strain as in battle-conditions, is less commonly the precipitating factor than in the case of the dysoxic states.

The mode of onset of the condition is often acute, and not uncommonly occurs in a man with a previously good personality and service-record. The first symptom may be a sudden episode of acute excitement, which may take the form of an impulsive attack on another person, or of a sudden attack of destructive violence. In other cases, the patient suddenly passes into an elated hypomanic state, with disjointed and nonsensical talk, peculiar actions and mannerisms, and evidence of bizarre delusions and hallucinations, under the influence of which outbursts of violence or homicidal attacks on others may occur. Occasionally, an impulsive suicidal attempt may be the first symptom.

In cases where the onset is insidious, the patient may first be noticed to be exhibiting the signs of a gradual personality-change. Thus, for instance, a man who has previously been well-adjusted and with normal interests is noticed by his comrades or N.C.O.'s to be gradually becoming solitary, morose, and asocial ; he may exhibit strange talk on subjects such as religion, sex, or psycho-

logy, or be noticed to be constantly reading the bible, or abstruse books on religious subjects, metaphysics, or other subjects quite foreign to his normal pursuits and inclinations. There may be episodes of peculiar behaviour, such as standing for long periods in one position, with the exhibition of bizarre mannerisms and stereotypy, or long periods of absorption in prayer or rumination. In patients whose phantasies take a religious turn, an acute visual hallucinatory episode of cosmic or apocalyptic content may be the first manifest symptom. It is not uncommon in some cases for the patient at this stage to report sick of his own accord, but more commonly he is referred to the unit medical officer by his N.C.O. or officer, whose notice has first been drawn to his peculiarities. Some patients, whose delusional material is of the religious type, may first draw attention to themselves by consulting the unit padre on bizarre and abstruse religious topics, or because of ideas of guilt and self-reproach connected with autoerotism.

In cases of the more intelligent type who have some degree of insight, the patient may report sick with a variety of vague somatic symptoms referred to his head, viscera, or genitals, or with complaints of feelings of anxiety and depression. At this stage, the diagnosis of an anxiety-state, hysteria, or even malingering may be made, and the man dismissed with a placebo, so that the true nature of the condition only becomes evident at a later stage, when the typical bizarre dysglycic symptoms become obvious. The occurrence of such vague symptoms of anxiety or hypochondriacal type in a man of previously cheerful and stable personality should therefore always be looked upon with suspicion and submitted to careful examination.

In a few cases, the patient may spontaneously report sick complaining of "voices in his head," feelings of influence, or other such obviously dysglycic symptoms.

Delinquency in the form of repeated absence without leave in a previously good soldier, disobedience, or aggressive language and behaviour towards a superior is occasionally a prodromal symptom, but it is more commonly found in the simple form of dysoxia. Similarly, progressive and insidious conduct deterioration in the form of apathy, slovenliness, and loss of interest are symptoms more typical of the malignant dysoxic states.

In cases where the precipitating cause is an acute infection, such as malaria or infective hepatitis, the dysglycia often commences as an acute confusional state which may be indistinguish-

able from a dysoxic confusion; this fails to clear up with the abatement of the febrile symptoms, and within a few days or weeks the bizarre hallucinations, delusions, and disordered behaviour typical of acute dysglycia begin to make their appearance.

In the form which occurs as the result of acute physical exhaustion, as in battle-cases, the prodromal symptoms may be practically indistinguishable from those of an acute hysterical confusional or battle-exhaustion state. The confusional symptoms, however, fail to resolve under rest and sedation, and the typical dysglycic features make their appearance within a few days. In the manic forms, however, the patient may pass straight into an acutely excited condition immediately following exposure to severe battle-stress.

Three main clinical types of dysglycia may be distinguished :—

(1) The simple or affective type, which corresponds to simple mania and hypomania in the orthodox classification. It is comparatively uncommon in military practice.

(2) The malignant or catastrophic type, usually termed hebephrenic schizophrenia in the orthodox nomenclature. Certain forms of confusional state are included in this group. It is by far the commonest form of dysglycia encountered in military practice.

(3) The sensory, or delusional type, corresponding to the paranoid or sensory form of dysoxia in age-incidence and general clinical features. It includes the conditions known in the orthodox terminology under the names of delusional insanity, paraphrenia, paranoia, dementia paranoides, and paranoid states.

As in dysoxia, atypical and anomalous forms are not infrequently found. These will be considered in detail in a subsequent chapter, and for the present only the typical or pure forms of the dysglycic syndrome will be considered.

(1) The Simple or Affective Type.

This will be dealt with first, as it is one of the two least common varieties in military practice. In its adolescent form, it tends to favour the younger-age group of 18 to 25 years; while, as the dysglycic component of the manic-depressive or cyclothymic encephalopathy, it is found chiefly affecting the older age-group.

The most typical form is, of course, the classical mania or hypomania of the text-books. The clinical picture is too well-known to require a detailed description, and the form encountered

under military conditions differs in no respect from that described in the standard text-books on mental disorders. The typical manic features are all seen, namely, euphoria and elation, flight of ideas, general acceleration of the stream of thought, hyperactivity, aggressiveness, and tendency to grandiose phantasy, and the course and prognosis are in all respects similar to the ordinary forms.

More commonly, a form is encountered in which the clinical features are those already described, with the addition of fleeting and ill-defined ideas of influence and passivity, autochthonous ideas, brief phases of confusion, and a certain fatuousness and childishness, which approaches that seen in the malignant form. There is, however, none of the wealth of bizarre hallucinations and delusions with association-disorder in its fully-developed form, as seen in the latter condition. This type of dysglycia rather resembles the simple form of dysoxia, except that elation and euphoria are substituted for apathy and depression.

The following case is a good example of this type :—

Case 10. An airman, aged 22, was admitted with a diagnosis of " schizophrenia," and history of excitable and erratic conduct, with childishness and general deterioration of conduct and efficiency. It appeared from the entries in his case-records that he had first been observed to be exhibiting abnormal conduct 18 months previously, when he was referred to an R.A.F. psychiatrist for an opinion ; apparently, the correct diagnosis had been missed, and he had simply been referred back to his unit with a recommendation for " firm handling and discipline." On admission, he was mildly elated, childish, and fatuous, and expressed no spontaneous complaints, beyond stating when questioned that " his nerves had been bad." Apart from this, he was unable to describe any symptoms, and was entirely without insight. His conduct varied between apathy with occasional fatuous smiling and periods of over-activity and aggressiveness. Orientation and memory were unaffected, and on impersonal topics his conversation was quite sensible. Aural hallucinations and ideas of passivity were not admitted, but his conduct at times suggested that these were present. He tended generally to be very evasive and guarded when asked about his symptoms. Physical examination was negative. He exhibited mild confusional phases at times. Electroanoxia and hypoglycæmia were both given, without the slightest

improvement, and he was finally discharged to the care of his relatives unimproved.

This case is a good example of an encephalopathy in which the disturbance was primarily in the sphere of affect and conduct, elation, fatuousness, hyperkinesia, and emotional deterioration being the prominent features, and entirely typical of the dysglycic form of brain-disease. The long history and signs of personality-deterioration explain the negative response to neurometabolic therapy.

(2) The Malignant or Catastrophic Form

This is by far the most common type of dysglycic reaction encountered under military conditions, as would be expected from its predilection for the military age-group. The common precipitating factors and modes of onset have already been indicated. It is the most important of the dysglycic disorders on account of its tendency to produce rapid and irreversible mental and physical degeneration so that the epithets "malignant" and "catastrophic" may justly be applied to it. It is also, however, the form of dysglycia which responds best of all to hypoglycæmia when treated early, and at the same time is one of the conditions which are most refractory to electroanoxia. Its clinical features are in all respects similar to those of the form encountered in civil practice, and its outstanding characteristics may be briefly listed as follows:—

(1) A peculiar and characteristic disturbance of the thought and associational mechanisms at the highest level, with motor excitement.

(2) A characteristic affective disorder, of which emotional incongruity and disharmony are the most prominent features.

(3) A wealth of bizarre sensory paræsthesias and hallucinations in all fields, frequently of the hedoniphronic type.

(4) Ideational disorder in the form of delusions of the bizarre, and grandiose type.

(5) A strong tendency to mental deterioration with irreversible cerebral changes.

(6) A specific responsiveness to hypoglycæmia, and complete lack of response to electroanoxia.

These six features may be regarded as the hallmarks of the dysglycic state. From the anatomical point of view, they may be looked upon as the clinical manifestations of a diffuse distur-

bance of the cerebral glycolysing mechanisms, affecting the thalamic and diencephalic regions, together with the whole of the cortical systems concerned in the functions of perception, integration of the higher thought-processes, conceptual thinking, insight, and judgment.

For general descriptive purposes, it will be convenient to discuss the clinical features of the malignant dysoxic state under the headings of thought-disturbance, the sensorium, ideation, motor and behaviour-disorders, affective abnormalities, and disturbances of the intellectual functions and field of consciousness.

The thought-disorder is the primary condition in all the dysglycic diseases, in contrast to the dysoxias, in which the affective disturbance is the primary disorder. It is seen in its most typical form in the malignant dysglycias, and has been described by various authors under such terms as "associational dementia, intrapsychic ataxia" (Stransky), "knight's move in association" (Mapother), and "dyssymbole" (Skottowe). Characteristically, it is present in a setting of clear consciousness, although clouding of consciousness frequently occurs as an associated feature in the acute forms of dysglycia, as it does in the dysoxic states.

In a typical case showing association disturbance, there is a rapid and disconnected flow of ideas, with speech closely resembling that of the manic type, but showing, in addition to acceleration of the stream of thought, gross disconnection and association-disorder. The resulting flow of speech is quite indescribable in ordinary language, and has to be actually heard to be properly appreciated. Bizarre expressions and neologisms are common, and irrelevance, verbigeration, and the constant repetition of peculiar words and phrases is often seen. Most characteristic is the peculiar disturbance of conceptual thinking termed by Skottowe "dyssymbole." This is the condition in which the patient is able to converse more or less rationally on impersonal topics, but shows a complete inability to express in intelligible language the gradations of his emotional experiences in the abstract sphere, although the higher-speech centres and thinking at the perceptual level are intact. The function of concept-formation in the abstract is, of course, the highest of all the cerebral functions and phylogenetically the latest developed, so that the dyssymbolic disorder represents a selective form of dementia at the highest level. It is partly a disturbance of the actual thinking-processes, and partly due to the peculiar

sensory disorder, as the result of which the patient experiences sensations which are quite indescribable in ordinary language, and so has to resort to the use of bizarre neologisms and expressions in his attempts to describe his feelings. Examples are such complaints as of " being electrically controlled by messages from the other world," or of " having a dictaphone in his head which records his thoughts." In short, in dysglycic thinking the concrete is substituted for the abstract, and this symptom can be experimentally reproduced very closely by poisoning with *cannabis indica* or mescaline. Alternatively, this symptom may present itself simply as a complete inability of the patient to describe his feelings and experiences at all, as is found in the dysoxic disorders. Thus, when asked the reason for his peculiar antics and mannerisms, the patient may rationalize by saying that he is " a bit upset at finding himself in hospital," or that " he feels a bit run down " ; or the question may be answered simply by a fatuous grin accompanied by some totally meaningless and irrelevant remark.

Another important characteristic of the dysglycic thought-disturbance is that his thought-processes are katathymic in type—that is to say, determined not by the ordinary impressions and experiences of the outside world but by his subconscious desires and hitherto repressed complexes, which are brought into consciousness as the result of the metabolic disorder in a manner similar to what occurs in mescal intoxication, and it is this peculiarity which gives rise to the bizarre and disjointed, apparently nonsensical stream of speech.

A profusion of bizarre hallucinations, both of the extracampine and intracampine types, is present in the majority of cases. In the acute forms, visual hallucinosis is common and coloured visions of fantastic type, often with a religious content, and similar to those of mescal or hashish-poisoning, are of frequent occurrence. More typical, however, are the aural hallucinations of complex type, commonly described as " voices," which may be located inside the head or coming from outside the body They frequently have a marked influence on conduct, and give rise to impulsive outbursts or homicidal episodes.

Somatic hallucinations are as frequent as the aural type, and are characteristically bizarre, and described by such terms as " electricity," " influence," " supernatural control " and so on. They are frequently referred to the genital organs but may also be referred to the brain, heart, or abdominal viscera.

Olfactory and gustatory hallucinosis, usually described as persecution by poisoned gas or fumes, or the patient's food and drink being "doped" or poisoned, are somewhat less frequently found than the three first types described.

The delusional material of dysglycic patients differs from that of dysoxics in the same way as the hallucinations. They are much richer in variety, interpreted in more fantastic terms, and are often of grandiose and hedoniphronic form as well as of the persecutory type. The grandiose delusions take the form commonly found in civilian practice, thus, the patient may believe he is Christ, is the Saviour of the World, or related to royalty. These ideas are often associated with the conduct-disorder. The ideas of passivity are usually described in much more bizarre terms than those of dysoxia. The patient may have delusions that he is under spiritual control, or is being interfered with by wireless, electricity, or telepathy These ideas are characteristically associated with the effective reaction of incongruity, fatuousness, and often elation and euphoria. This clinical picture is in marked contrast to the dull, depressed, and perplexed reaction of the dysoxic patient. Ideas of guilt, bodily disease, and impending death are much less typical of dysglycia than of the dysoxic states. Peculiar bodily sensations with feelings of changed personality or bodily change are also common in dysglycics, and are associated with the typical emotional reaction just described.

Clouding of consciousness, with disorientation in time and space and varying degrees of amnesia, is common in the acute dysglycic state. This again contradicts the common assertion of most textbooks that dysglycic phenomena usually occur in a setting of clear consciousness. The mental confusion is one of the first symptoms as a rule to ameliorate under hypoglycæmic therapy. In addition to the mental confusion, states of ecstasy, unreality, and double orientation are often found, usually in association with religious delusions and hallucinations. Subjective feelings of unreality or altered personality, however, are not common, and are more often found in hysterical and anxiety conditions than in the metabolic encephalopathies.

On the motor side, acute maniacal states with excitement, pressure of activity, impulsive outbursts, destructiveness and faulty habits, are the rule in the acute form. Absolute insomnia with negativism and refusal of food are very common. A variety of bizarre mannerisms, with grimacing, stereotyped

movements and attitudes, often associated with ecstatic states, is frequently seen. Katatonic rigidity with flexibilitas cerea may be found, as in the katatonic form of dysoxia, although it is much less common than in the latter condition. Sudden and impulsive suicidal attempts are not uncommon, and are usually found in those cases with marked dyssymbolic features as a reaction of terror and despair at the peculiar and indescribable mental feelings. They are particularly liable to occur in cases with rapidly alternating phases of elation and depression, in which judgment and insight are as yet to a certain extent unimpaired.

The affective reaction of dysglycia contrasts strikingly with the dull, perplexed, and dysphoric state seen in dysoxic patients. It may be of the frankly hypomanic or manic type, with elation and euphoria ; most characteristic is the peculiar fatuousness and silliness, which is often associated with a peculiarly pompous and exalted manner of speech and gesture. It may vary from the exalted and elated form to an indifferent and fatuously complacent state, this last reaction being commonly seen in cases of fairly long duration, in which some degree of mental deterioration has set in.

Affective incongruity is particularly well seen in malignant dysglycia, with its alternating phases of fatuous grinning and smiling, and outbursts of causeless weeping. Dysglycic apathy and indifference are commonly secondary to preoccupation with bizarre hallucinations and phantasy, and not, as in the case of dysoxia, a primary affective disorder. The importance of this symptom in connection with the problem of differential diagnosis will be referred to in a later chapter.

In some cases, however, where personality and insight are not too greatly impaired, the patient may display marked fear, perplexity, and apprehension as a secondary reaction to the strange and often terrifying paræsthesias and hallucinations, so that on superficial examination the emotional reaction may bear a strong resemblance to that of the dysoxic state.

The following three cases are typical examples of the acute catastrophic form of dysglycia :

Case 11. An airman, aged 23, was admitted with a history of having for several weeks exhibited peculiar behaviour, with bizarre religious ideas and auditory hallucinations. On admission, he was acutely excited, maniacal and restless, and elated and fatuous, with a marked flight of ideas, hyper-

kinesis, destructiveness and dirty habits. Physically he was cachectic, toxic, and emaciated. He displayed mannerisms, attitudes and grimacing, with periods of religious ecstasy. The response to insulin therapy was rapid and dramatic both as regards the mental and physical symptoms. He finally made a good recovery with insight, and was discharged in a state of remission. When last heard of, he was at his home in Canada, and keeping well. He received altogether a total of twenty insulin comas.

Case 12. A gunner, aged 20, was invalided from Italy with a history of having developed delusions that he was about to be condemned to death and shot. On admission he was well-behaved, but childish and fatuous and showed no insight. He exhibited a considerable degree of apathy, mannerisms, and constant inane grinning and giggling, and there was marked affective shallowness and incongruity. He showed no evidence of disorientation. He was aurally hallucinated, and expressed delusions that he was going to be court-martialled and shot. The physical examination was negative. He received a course of electroanoxia without any improvement, but made a good remission following hypoglycæmia and was discharged to his home recovered, a total of 21 comas having been given.

This case would appear at first sight to be one of the dysoxic type, on account of the persecutory hallucinations and ideas of impending death. The characteristic affective reaction and response to electroanoxia and hypoglycæmia, however, indicate beyond doubt that this patient was a case of true dysglycic type.

Case 13. A flight-sergeant, aged 28, with ten years' regular service and an excellent record, was admitted with a history of having in the last few weeks developed delusions of a religious nature and erratic conduct. He had been noted as previously having had rather unusual tastes, such as philosophy and religious subjects. His breakdown had followed a prolonged period of overwork in administrative duties which involved heavy responsibility. On admission, he presented all the features of a fulminating dysglycic state. He was fearfully emaciated, and quite literally skin and bones, toxic and cachetic, with foul breath, earthy pallor, intense dehydration, and a foul-smelling nasal discharge. Bedsores were present on the heels and sacrum. His mental state

alternated between periods of typical katatonic stupor and outbursts of noisy, destructive, and maniacal behaviour, with flight of ideas, vivid visual and aural hallucinosis, fantastic religious delusions, and feelings of influence and control. He was doubly incontinent and required tube-feeding daily. Shortly after admission, he developed a severe attack of cardiovascular syncope, requiring intravenous coramine and general stimulative measures. He was started straightway on hypoglycæmia, commencing with doses of ten units, the dosage being increased very cautiously. Coma-level was finally attained at the very low dosage of ten to twelve units, and the response was dramatic, both in his mental and physical conditions. He eventually made a complete recovery with good insight, was discharged to duty at his own request and has remained well since.

This case is a good illustration of the severe physical symptoms of toxæmia which may be found in association with the acute dysglycic states, and of the extraordinary rapidity with which these patients may deteriorate when untreated. It also illustrates the importance of vigorous and immediate therapy in these cases, which should always be regarded as acute medical emergencies. It is also a good example of how apparently dysoxic symptoms in the form of alternating periods of stupor may sometimes colour a dysglycic picture and at times confuse the diagnosis; the elation, overactivity, and wealth of visual hallucinations and religious delusions, however, were all features completely typical of the dysglycic state. This point will be further discussed in a later chapter in connection with the anomalous or mixed forms of metabolic encephalopathy which are sometimes encountered.

The above three cases illustrate perfectly the clinical picture of the malignant dysglycic form of brain-disease, with its peculiar affective reaction, variety of productive symptoms, and pathological hyperactivity, which contrasts strikingly with the dull, retarded, depressed, and underproductive state seen in the series of dysoxic cases of the malignant type described in the previous chapter. The response to hypoglycæmia and characteristic failure to react to anoxic therapy, in contrast to the dysoxic form of disorder, is also very striking. Cases 11 and 13 are typical examples of the most acute and fulminating type of dysglycic reaction, while Case 12 represents the subacute form of more insidious onset and rather longer duration.

(3) The Paranoid Type of Dysglycia

The paranoid or sensory form of dysglycia includes the conditions known as paranoia, or systematized delusional insanity, and paraphrenia, or non-systematized delusional insanity, in the orthodox terminology. It also includes the heterogeneous states termed variously dementia paranoides, paranoid schizophrenia, paranoid states, and hallucinatory-paranoid psychoses. Of these conditions, the systematized delusional form is as rare in military as it is in civilian practice, so that it can be dismissed without further consideration. Having its onset as it does in the later-age period of 35-40 years and over, it is only reasonable to expect that it will be rarely encountered in its typical form among the usual military age-groups. The writer has seen only two cases (one of which was doubtful) in the whole of five years of his military psychiatric experience.

The non-systematized form is also comparatively uncommon in comparison with the malignant form. Its age-incidence is in the older group, 35 years and over, and its clinical aspects are in all respects similar to those of the type encountered in civil practice. It is distinguished from the malignant dysglycias by the following characteristics—the later age of onset, gradual evolution, absence of the peculiar language and conduct-disorder, and little tendency to produce dilapidation of the personality. It corresponds to the paranoid type of dysoxia, in being primarily a disorder of the centres concerned in the functions of perception at the higher levels and interpretation of external stimuli. As it has little or no tendency to produce dementia, the end-result is a chronically hallucinated and deluded patient with fairly well-preserved personality, rather than the demented, wet, dirty, and degraded type seen commonly as the final product of a malignant dysglycia. Confusional features are usually not common.

The onset being in most cases of gradual evolution, the patient is most likely to be brought to the psychiatrist on account of abnormal conduct observed at his unit. The commonest early symptoms are repeated disciplinary offences, such as absence without leave, peculiar and abnormally seclusive habits, aggresive outbursts while the patient is under the influence of his delusions, or sometimes an acute excited episode. It is extremely rare for this type of dysglycia to be precipitated as an acute reaction by severe stress, as in the case of the malignant dysoxic and dysglycic disorders.

The usual clinical picture is that of a well-preserved personality with well-marked hallucinosis and delusional features. The hallucinosis is almost always of the aural and somatic type, and the delusions either persecutory, grandiose, or often both. The emotional reaction is usually appropriate, and may be exalted and elated in the grandiose type, or querulous, suspicious and anxious, often associated with aggressive outbursts and homicidal tendencies, in the persecuted form. The incongruity and fatuousness of malignant dysglycia, and the depressed, confused reaction of the dysoxic are absent.

Paranoid dysglycia may, like its dysoxic counterpart, be regarded as a disorder of the sensory and higher thought-centres of the brain. Anatomically, this means that the dysglycic process is confined principally to these areas, while sparing the diencephalic centres, with the result that gross autonomic changes, toxæmia, and personality deterioration are not found, unlike what occurs in the malignant form. Thus it is to be expected that the clinical symptoms will be chiefly elaborate hallucinations, auditory and visual illusions, and misinterpretation of perceptions with consequent delusional formation. Dyssymbolic features are seen in this form principally as bizarre paræsthesias and language-disturbance with peculiar neologisms, used by the patient in his attempts to describe his abnormal mental experiences. Paranoid dysglycia is, like the other dysglycic syndromes, primarily a disorder of the thinking-processes, the emotional reaction being largely secondary to this ; whereas the dysoxic states are primarily affective disorders, the nociphronic delusions and hallucinosis being secondary to the depression. The emotional reaction in the paranoid form of dysglycia naturally varies according to whether the delusional and hallucinatory material is pleasant or unpleasant.

The following two cases typify the condition fairly well :—

Case 14. An airman, aged 30, was admitted with a history of the onset in the last three months of grandiose delusions and of having made an impulsive attack on his unit medical officer on the day prior to admission. On examination, he was well-behaved and talked rationally on ordinary topics, but was emotionally flat and detached in manner. He stated in a matter-of-fact tone of voice that he was the rightful Duke of Marlborough, and was receiving wireless messages to this effect from the B.B.C. He showed numerous bizarre ideas of influence and auditory hallucinations of this type, and

his insight and judgment were grossly defective, although orientation and memory were intact. The only other abnormalities noted were a mask-like almost parkinsonian facial expression and an effeminant, mincing manner of speech. The blood Kahn test and C.S.F. were negative. He received a course of hypoglycæmia with 19 comas, and made a good remission with fair insight. He was discharged to his home and apparently remained well for about three months; subsequently he was reported as having relapsed and again become apathetic and deluded.

Case 15. A private, aged 39, was admitted with a history of the gradual development of delusions and ideas of reference for the last $2\frac{1}{2}$ years. On admission, he was well-behaved, co-operative, and showed no gross disorder of thought or language. He was grossly deluded, however, and believed that people made remarks about him, spread disparaging statements about his record, made signs at him behind his back and that his description was being circulated to the various police-stations in the neighbourhood. Physical examination showed nothing beyond defective vision in the left eye and an old-standing right otitis media. He made a good response to hypoglycæmia, and was discharged in remission, but within a few days of leaving hospital he relapsed and became hallucinated and deluded, and has remained in this condition since that time.

These two cases are typical in age-incidence, symptomatology, and neurometabolic response. The good immediate therapeutic result in Case 14 was undoubtedly due to the fact that the encephalopathy was of recent onset, and illustrates how even in these delusional encephalopathies, which before the advent of neurometabolic therapy always had an ominous prognosis, much can be done by early and energetic treatment. The poor result in Case 15 was undoubtedly due to the long history of the disease.

It should not be supposed from the above clinical descriptions that there is any hard and fast line of distinction between the malignant and sensory forms of the dysglycic syndrome, since a number of clinical features may be common to both diseases. Thus, for example, confusional episodes with motor signs and visual hallucinosis may occur in the acute exacerbations of the delusional form, while, in the malignant type after the acute phase has subsided, a predominantly delusional clinical picture

may be left as the residuum. Acute manic episodes may in the same way be found in both types of disorder.

The atypical forms of dysglycia will be described and discussed in the ensuing chapter under the subject of differential diagnosis of the two main types of metabolic encephalopathy.

CHAPTER VII

DIFFERENTIAL DIAGNOSIS AND ATYPICAL FORMS

(1) The differential diagnosis of the metabolic encephalopathies may be conveniently considered under two headings; firstly, the diagnosis of the two main types from one another, and secondly, the diagnosis of the metabolic group of brain-disorders from other conditions which may simulate them, such as neurotic conditions and organic and degenerative encephalopathies. For the present, the first alone will be considered in this chapter. The importace of early and accurate diagnosis between the two main types will be evident from a consideration of the subject-matter of the two preceding chapters, particularly from the point of view of the institution of appropriate specific therapy at the earliest possible moment. Failure to make a correct diagnosis in the early stages may not only involve much waste of time and trouble in giving the wrong kind of treatment, but may also seriously prejudice the patient's chances of recovery at the time when specific therapy offers the best hope of a favourable outcome.

The diagnosis of dysoxia from dysglycia would at first sight appear a simple matter if all the syndromes met with showed the typical dysoxic or typical dysglycic features as described in the two preceding chapters; thus, the symptoms would always go by opposites—for instance, excitement and elation, dysglycia; depression and retardation, dysoxia, and so on. This is, however, by no means invariably the case, as is exemplified in many other branches of medicine. Thus, for example, typical pneumonia and typical measles, like typical dysoxia and typical dysglycia, offer no great diagnostic difficulty, whereas on the other hand the atypical forms may be extremely puzzling and difficult to detect without the most careful observation. In the same manner, mixed and atypical forms of the dysoxic and dysglycic syndrome are not infrequently found, whose symptomatology does not appear at first sight to fit in with either of the two, or to conform to the clinical criteria laid down in the previous chapters.

Before proceeding to discuss the diagnosis of the individual symptoms, two important points should first be stressed. The first is the distinction between symptoms which are primary, and those which are purely secondary. It should always be

borne in mind that in dysoxia the affective and volitional disorder is the primary disturbance, the delusions and hallucinations being secondary to this, while in dysglycia, the underlying condition is the disorder of thinking and the sensorium, while the affective response is largely a secondary reaction to this. The second is the importance of the type of emotional response associated with the sensory and ideational abnormalities. It will be apparent from the description in the previous chapter that the emotional response of the dysoxic is strongly appropriate and consists of dysphoria in a setting either of apathy and perplexity, or of tension and apprehension, whereas that of the dysglycic is one of elation, euphoria, and excitement, often with fatuousness and affective incongruity. The apparent exceptions to this rule will be presently discussed in detail. The third is that the diagnostic criteria already laid down are only applicable in many respects to early cases, that is, to cases in which secondary dementia has not occurred. In the type of patient in the chronic wards of a civilian mental hospital the clinical picture is often blurred and distorted by secondary deterioration ; thus, for example, a deteriorated dysglycic of many years standing may exhibit apathy and dullness in all respects similar to that found in typical dysoxics, and the same is often true of choronic paranoid patients, both of the dysoxic and dysglycic types. The fourth and most important point in the diagnosis is the response to neurometabolic therapy, which is specific for each of the two types. It is the response to anoxic and hypoglycæmic therapy rather than the symptomatology of any given case which decides under which of the two main types it should be placed.

It will be evident from the clinical descriptions already given that certain individual symptoms are common to both forms of encephalopathy, and the question of the differential diagnosis may be most conveniently considered by examining these symptoms in their order of frequency. The most common encephalopathic symptoms encountered in early cases are, in order of frequency of occurrence, dysphoria, mental confusion, delusions, hallucinosis, and disorders of the content and stream of thought, and these will now be considered severally in this order.

Depression in its various forms is the commonest single symptom encountered in military psychiatry, and an extremely common one in civilian practice. In the under 30 age-group, the commonest single cause of an endogenous depression is the malignant form of dysoxia. The benign or manic-depressive

form of dysoxia is not a common cause in this age-group, and it may be categorically stated that this diagnosis should only be made when the patient is over 35 years of age, and there is a history of one or more previous depressive or manic episodes with spontaneous remission. A diagnosis of benign dysoxia (i.e., manic-depressive syndrome) in a patient under 30 years of age should always be looked upon with the greatest suspicion. In a malignant dysoxia which commences as an apparently simple endogenous depression, the usual sequence of events is as follows ; the depression and anxiety are in the course of a few weeks gradually replaced by the dull perplexed reaction typical of malignant dysoxia, with recurrent attacks of confusion, and the emergence of aural hallucinosis and delusions of reference as the disease progresses soon reveals the true nature of the condition. A series of prompt remissions following electroanoxia, followed as promptly by relapses, further confirms the diagnosis.

Anxiety, tension, and apprehension may also occur as secondary symptoms in the early stages of a slowly evolving dysglycic state. In the very early stages of this disorder, while there is still some insight and the patient's personality and affective responses are still well-preserved, a typical anxiety-pattern may be the patient's response to the bizarre and frightening sensations which he experiences, and at this stage a sudden and impulsive suicidal attempt may occur. Similarly, a depressive reaction may be the emotional concomitant of obsessional autochthonous ideas and rumination of an unpleasant character. This is commonly found in the more intelligent and sensitive individual in whom insight and judgment are as yet comparatively unimpaired. and it is often found in these cases that the secondary anxiety-symptoms may completely obscure the primary dysglycic features and possibly lead to a diagnosis of dysoxia or neurotic depression. In these cases, the underlying condition may be revealed by careful psychiatric examination on admission, or it may only become evident after a considerable period of observation, when the typical dysglycic symptoms gradually unfold themselves.

In dysglycics where the condition has been of gradual evolution or has reached the chronic stage, the prevailing emotional reaction may be one of apparent apathy with mild depression and bradyphrenia—in other words, a condition of affairs exactly similar to what is seen in the simple or malignant form of dysoxia. Superficial examination of a case of this type might therefore lead to a diagnosis of the latter condition ; but a careful examination

will show that the apathy and detachment are secondary to preoccupation with bizarre phantasies and hallucinations, and not a primary affective reaction as in dysoxia.

The following two cases are good examples of this atypical form of dysglycia :—

CASE 16. A driver, R.A.S.C., aged 22, was invalided from the Middle East with a history of acute encephalopathic breakdown of katatonic type while serving in Cyprus in 1943. On admission, he showed signs strongly suggestive of a typical malignant dysoxia. He was completely mute, stuporose, inaccessible, and retarded, and tended to wander in an aimless and confused manner about the ward, showing no evidence of interest in his surroundings. Ideas of guilt and self-reproach were present ; he was deluded that he had venereal disease, was dead and about to be judged for his sins, and expressed a variety of bizarre religious ideas. Aural hallucinosis of accusatory type was present, and he exhibited periodic phases of confusion, with rambling and incoherent speech. Physical findings were negative. He received a course of electroanoxia with transient improvement only, and never complete remission. After his first relapse, hypoglycæmia was started ; the response was immediate, and he finally made a good remission with insight.

This case exemplifies how, in some cases of dysglycia which have been allowed to deteriorate, the symptomatology may be completely misleading ; the affective reaction, type of hallucinosis, and delusional material in this case would at first sight appear to be typically dysoxic ; but the bizarre nature of the ideational and sensory features together with the response to specific therapy show beyond doubt that this patient was one of the pure dysglycic type. The value of the neurometabolic response as a diagnostic test is also illustrated very well in this case which shows how in some of these atypical forms it may be the only sure diagnostic criterion.

CASE 17. A private, aged 26, was invalided from the North African front, with a history of several months progressive personality-deterioration, increasing dullness, slovenly habits, and general uselessness as a soldier. When first seen, he was simple, fatuous, and childish, and exhibited constant grinning and causeless laughter. Aural hallucinosis and ideas of reference were present, he gave a very poor account of of himself, and showed defective memory and periods of

confusion and disorientation with aimless restlessness of apparently typical dysoxic form. Physical findings were negative. A course of electroanoxia produced little or no real improvement, but following hypoglycæmic therapy he made a good recovery. A mild degree of mental defect was apparent in this case.

The salient dysglycic features of this case were the fatuousness and emotional incongruity, the dullness and mental confusion being purely secondary features. The neurometabolic response was in every way typical of the dysglycic state. The term "pseudo-dysoxic dysglycia" might well be applied to this type of patient.

The next symptom to be considered is the confusional state. One of the commonest problems in diagnosis is that of the patient who is admitted in a state of stupor and mental confusion, both of which conditions may conveniently be considered together. They may occur as initial symptoms of both the acute dysoxic and dysglycic states, and their importance is that they render the patient inaccessible to psychiatric exploration and so completely mask the true nature of the underlying condition.

Dysglycic confusional states are commonly associated with alternating maniacal phases, impulsive and destructive outbursts, the typically bizarre and elated affective reaction, hyperkinesis, and a variety of delusions and hallucinations, usually of grandiose and hedoniphronic type. It may generally be stated that, if these features are present, the diagnosis of dysglycia may safely be made, even when they alternate with periods of dullness and stupor. Case 13 is a good example of this form of dysglycia.

In acute dysoxic confusion, the points to look for are the dull, retarded, depressed, and apathetic reaction, with ideas of guilt and self-reproach, associated with hallucinosis of nociphronic type. In the katatonic form, the signs of rigidity and *flexibilitas cerea* are seen in addition, but the most common form is the depressive-confusional type without dyskinetic features. In dysoxia simplex, the predominating features are those of apathy and progressive withdrawal from reality, the stupor and confusional features being often more apparent than real, and largely secondary to the emotional and volitional deterioration.

Generally speaking, it may be laid down that the presence in a patient under 30 years of age of acute confusional features in association with a depression of encephalopathic type indicates that the condition is one of malignant dysoxia, and that this

rule holds good even when there is a history of one or more previous attacks of manic-depressive type with spontaneous remission.

The diagnostic points between the malignant and benign types of dysoxia may be briefly summed up as follows. Benign dysoxia is much less common, it occurs in the later age-group, and there is commonly a history of previous attacks of excitement or depression with spontaneous remission. It is not usually associated with hysterical symptoms, whereas in certain forms of malignant dysoxia (the hysterœncephalopathic form) hysterical features may be found in association with the dysoxic syndrome. In benign dysoxia, confusional signs are not common, whereas in the malignant form the confused, perplexed state with dyssymbole, or inability to describe symptoms in intelligible language, is the rule. Benign dysoxia requires fewer anoxic treatments to effect remission than the malignant form, and there is much less tendency to relapse and progression of the disorder to mental deterioration. In the benign form, katatonic signs with conduct-disorder and faulty habits are very rare, whereas in malignant dysoxia they are the rule. Mental defect is more likely to be found in association with the malignant form, while patients who develop the benign type of reaction are often of superior intelligence and good previous personality-type.

The following case illustrates the difficulty which may sometimes arise in differentiating the two forms, and the value of the anoxic response as the only reliable diagnostic test in such cases :—

> Case 18. A sergeant, aged 28, was admitted from a home-station, with a history of recent onset of acute depression and mental confusion. On admission, he was dull, stuporose, confused, and acutely depressed, and marked retardation, with an expression of bewilderment and perplexity, and rambling, disjointed speech were prominent features. He expressed pronounced ideas of guilt and self-reproach, and phases of nocturnal restlessness were present. Physical examination was negative. As no signs of spontaneous improvement were evident, electroanoxia was commenced within a few days of admission. At first he showed very little response, but eventually made a good recovery with insight after a total of 9 convulsions.

This patient's age and general clinical features were strongly suggestive of a typical malignant dysoxia. Exploration of the past history, however, revealed when he became accessible that

he had had several mild depressive episodes in civilian life, all of which were followed by spontaneous recovery. The final diagnosis in this case, therefore, was benign dysoxia.

The delusions and hallucinations may be conveniently considered together. Grandiose and bizarre hallucinations and delusions are much more characteristic of dysglycia, but the persecutory type with feelings of influence and control may be common to both. In the differentiation of dysoxic from dysglycic hallucinatory-delusional phenomena, the accompanying emotional reaction and conduct disorder are of more importance than the actual type of sensory disorder. As previously indicated, the hallucinosis and delusions of acute dysoxia are fleeting and evanescent as compared with those of dysglycia, and are largely secondary to the affective disturbance; in dysglycia on the other hand, they are part of the primary disorder of perception and conceptual thinking.

In the predominantly delusional type the sensory disturbance is the primary disorder; in this type of encephalopathy the perceptual disturbance, in the form of misinterpretation and distortion of normal enteroceptive and exteroceptive sensations, appears to be the underlying primary disorder. The presence of a clear setting of consciousness and the absence of the language-disorder characteristic of malignant dysglycia are also reliable diagnostic signs.

The motor anomalies may be considered next. Apathy, psychomotor retardation, poverty of movement, stupor of simple katatonic type, and restless confused wandering are all symptoms typical of the dysoxic state. In contrast to this, pressure of activity, maniacal excitement, bizarre mannerisms with grimaces and stereotyped movements, destructiveness, and homicidal tendencies are much more typical of dysglycia. Symptoms such as insomnia, nocturnal restlessness, incontinence, negativism, and refusal of food are common to both, and have no diagnostic significance.

In dysoxias, especially of the katatonic type, the patient often assumes a characteristic attitude when undisturbed in bed; he lies on his back with the shoulders raised from the pillow, the head being inclined forward on the chest, the facial expression being a blank and abstracted stare. This position may be maintained with no evidence of spontaneous activity for several hours on end. This sign is also not uncommonly found in the simple form of malignant dysoxia.

The disorders of thought have already been fully dealt with. Elation, flight of ideas, conceptual and association disorder, and acceleration of the thought-processes, are characteristic of the simple and malignant forms of dysglycia. Bradyphrenia, with thought-blocking, retardation and poverty of ideation are found in all varieties of dysoxia except the paranoid type. It is in the thought-disorder that the contrast between the dysglycic and dysoxic states is most strikingly illustrated.

The important dyssymbole-sign is common to both types. In both forms it may show itself as inability of the patient to describe his sensations, especially in the acute dysoxic reactions. In malignant dysglycia, it commonly takes the form of bizarre language with associational disorder and the use of neologisms, and this sign is a reliable diagnostic feature of the latter condition.

(2) The Atypical and Mixed Forms

The clinical descriptions presented in the last chapters are those of the typical dysoxic and dysglycic syndromes as seen in their pure form. Thus, at one end of the scale we have the typical pure dysoxia with its four cardinal features of depression, apathy, retardation and nociphronic hallucinations and delusions, and at the other end the pure dysglycias, with their cardinal symptoms of elation, psychomotor acceleration, over-activity and hedoniphronic hallucinations and delusions. A more striking contrast in symptomatology could hardly be found anywhere in the whole of medicine.

As generally occurs in medicine, however, there are found in between the two groups cases of an intermediate type, which do not conform exactly to either, but show a mixed or atypical symptomatology. These may be divided into two groups; the first group might be termed the alternating or circular type, in which episodes of dysoxic depression alternate with periods of dysglycic excitement. Of this type the classical form of manic-depressive encephalopathy is an example. Another is the form of hebephrenia with alternating phases of apathy and dullness and excitement with bizarre hallucinations and delusions. The second group of cases comprises those which show a mixture of dysglycic and dysoxic symptoms throughout.

The therapy of this form presents a rather more complex problem than that of the pure forms. As we have seen, the pure dysoxias are the most sensitive to anoxic therapy and the most

resistant to hypoglycæmia, while on the other hand the pure dysglycias are most sensitive to insulin and most resistive to anoxia. The greater the degree of retardation and depression, the more striking is the response to anoxia, while the greater the degree of elation and psychomotor acceleration, the more striking is the response to hypoglycæmia. In simple language, the sadder the patient the better is the anoxic response, while the madder the patient, the better is the response to hypoglycæmia.

It would be expected from a consideration of these facts that the alternating form would respond best to anoxia while in the dysoxic phase and to insulin when in the dysglycic phase, while the mixed form would show a response between that of pure dysoxia and pure dysglycia, the relative sensitivity to anoxia and hypoglycæmia varying according to whether the dysoxic or dysglycic symptomatology prevailed. This is actually what occurs in practice, so that the difficulties encountered in the treatment of these mixed forms will at once become apparent, and will be dealt with more fully in the chapter dealing with the technique of neurometabolic therapy.

The usual response of the mixed form to specific therapy is a temporary and moderately good response of the florid symptoms to anoxia, with either partial relapse on cessation of this therapy, or persistence of the thought-disorder and delusions of dysglycic type, these symptoms having now become apparent when the overlying dysoxic signs have been removed. If the case has been treated first by hypoglycæmia, the dysglycic features in the form of fatuousness, bizarre delusions, and hallucinations may be abolished first leaving residual dysoxic signs, such as slight dullness, apathy, and mild depression, which subsequently clear up on the exhibition of a course of electroanoxia. Occasionally, in a case of this type the patient may, as the result of anoxia administered while in the dysoxic stage, be precipitated straight into a phase of dysglycic excitement.

The alternating form of encephalopathy presents little difficulty in diagnosis, its hallmark being the occurrence of alternating periods of dysoxic depression and dysglycic excitement.

The presence of a mixed form of encephalopathy should be suspected in cases where apathy, dullness, and a complacent attitude without dysphoria are found in combination with hallucinations and autochthonous ideas of bizarre dysglycic type, particularly if the case shows a poor response to anoxic therapy. In an insulin-treated case, persistent apathy and mild depression

which fails to improve after florid dysglycic features have resolved are always suggestive of a mixed encephalopathy. The sudden onset of a phase of restlessness and excitement with bizarre hallucinosis and delusions in a previously depressed and apparently dysoxic patient is always a sure sign that the case is not one of pure dysoxia.

The following cases illustrate well the rather confusing mixture of symptoms and the characteristic response to neurometabolic therapy encountered in these cases.

Case 19. A gunner, aged 24, was invalided from the Middle East Forces with a history of depression, aural and visual hallucinations, deterioration of conduct, and attempt at suicide. He had a previous history of neurotic tendencies in civil life. On admission, he was childish, fatuous, and showed hallucinations with ideas of control and influence. Marked affective incongruity with inane smiling and laughing, autochthonous ideas and mild phases of confusion were prominent features. The physical findings were negative, and his mental features appeared to be predominantly of the dysglycic type. His hallucinations and other florid features improved considerably under insulin, but on termination of the treatment he was only moderately improved, and still showed fatuousness, emotional incongruity, and irritability. Shortly after termination of insulin therapy, he made a sudden attempt at suicide by drinking a bottle of oil. When questioned, he admitted a return of autochthonous ideas and suicidal impulses. Following a course of anoxia, he showed a considerably greater degree of improvement than with insulin, was much brighter but remained emotionally facile and very childish and manneristic. Within a week or so of completing his course of electroanoxia, he became confused, fatuous and hallucinated with alternating periods of depression and powerful suicidal impulses. After a further course of hypoglycæmia, he again showed marked improvement, and was discharged to the care of his relatives much improved.

Case 20. A driver, R.A.S.C., aged 31, was invalided from Italy with a history of an acute paranoid type of breakdown with phases of acute excitement. On admission, he presented the features of an acute manic state. He was noisy, aggressive, threatening, and resistive, and generally suspicious and antagonistic in attitude. His affective response was on the whole one of irritable elation; this state alternated with

periods during which he was quieter and more tractable, but fatuous, rambling, and disjointed in speech, and showed vague and fleeting ideas of persecution, aural hallucinosis, and complete inability to express his thoughts and feelings in intelligible language. The physical findings were negative. A course of electroanoxia produced transient improvement only; following a subsequent course of insulin, he improved considerably and was discharged to the care of his relatives in social remission, but still showed residual symptoms in the form of some degree of fatuousness and emotional facility, partial insight only being present.

Case 21. An airman, aged 22, was invalided from India, with a history of about three months' duration of delusions of persecution by Nazi agents, and an impulsive attempt at suicide by stabbing himself with a table-fork. On admission, he was dull, detached, retarded, and apathetic, with katatonic features in the form of grimacing and peculiar antics and mannerisms. Aural hallucinosis of persecutory type and delusions of the type described in the history were present. The physical findings were negative. His electroanoxic response was very slight, but following insulin therapy he made a good remission, and was discharged to his home recovered.

The three cases described above are good examples of the mixed form, in which a simultaneous combination of dysoxic and dysglycic features is found. In each case the type of neuro-metabolic response indicated that the encephalopathy was preponderantly of dysglycic type, although a strong admixture of dysoxic symptoms was evident.

The second group, in which alternating dysoxic and dysglycic phases occur, is illustrated by the following case :—

Case 22. A flight-sergeant, R.A.F., aged 25. He was invalided from North Africa with a history of 11 to 12 months' duration of delusions of reference and aural hallucinosis. The precipitating factor was apparently his trial by general court-martial for a serious offence, of which he had been acquitted, but which was followed by acute depression. When first seen, his symptoms were of predominantly dysoxic type. He was dull, apathetic, detached, and with marked emotional flattening and defective insight, and displayed ideas of reference and aural hallucinations. Physical findings were negative. He alternated between this condition and phases

of excitement, elation, and fatuous euphoria, with delusions and hallucinosis of religious type, and occasional maniacal and impulsive outbursts. He made a poor response to electroanoxia, but responded dramatically to hypoglycæmia, tending, however, to relapse very quickly as soon as this treatment was discontinued. He was finally discharged to the care of his relatives improved, but still showing dysglycic signs in the form of fatuity, hallucinosis, and defective insight.

This case is a good example of the atypical form of dysglycia, in which the dysglycic features were masked by overlying symptoms of apparently dysoxic type ; the response to treatment was typically dysglycic, the indifferent therapeutic result being undoubtedly due to the long duration of the disease.

(3) The Derealization-Depersonalization Syndrome

This condition has been described as a clinical entity by several writers, notably Maclay and Guttman in their account of the psychological effects on the symptoms produced by the exhibition of small doses of mescaline. From the point of view of classification, it should rightly be regarded as a special form of the dysoxic syndrome, but in view of its markedly aberrant clinical features it has been included by the writer among the atypical forms of this disease.

Its mode of onset and causal factors are the same as those described for the ordinary forms of encephalopathy. The principal symptom, as the name implies, is the subjective feeling of changed personality and unreality. This symptom may present itself in two forms—derealization, or a feeling that the outside world is changed and has become unreal, and a feeling of the patient's self having become altered. Two other notable symptoms are present, namely a marked degree of depression, and a peculiar and distressing sensation referred to the head, and this triad of symptoms may be considered to be the hallmark of the derealization syndrome. It resembles typical dysoxia in that it is markedly responsive to electroanoxia, but differs from that condition in the following respects.

The condition is present in a setting of clear consciousness, and the patient's rapport and insight are unimpaired. There is a remarkable absence of " insane " features, such as delusions, hallucinosis, conduct-disorder, and retardation, and there is no tendency to mental deterioration. The syndrome would thus appear to resemble more closely in its general features the

hysterical and psychoneurotic states, but gross conversion-symptoms and anxiety-signs are absent. It is entirely refractory to psychotherapy, as also to symptomatic measures such as the administration of bromides or cerebral stimulants, while it obeys the encephalopathic rule of being made worse in the great majority of cases by the administration of powerful euphoriants ; this fact has been demonstrated by the experiments of Guttmann and Maclay on the effects of mescaline sulphate in a series of these cases. Also, unlike hysteria and neurotic depression, it tends to occur almost exclusively in sensitive personalities of superior intelligence, particularly in those of the rigid, overscrupulous, and obsessional type.

The cardinal symptom, that of derealization, is variously described by the patient as a feeling of " being in a daze," " in a state of trance," " changed personality," or a feeling " that he will never be the same again." Usually, the patient says that he feels the outside world appears far away or unreal, or that he himself seems changed in some strange way ; very often, the patient seems to find great difficulty in describing his state in ordinary language, although the bizarre form of dyssymbole seen in typical dysglycia is absent. The general emotional reaction is one of distress, puzzlement, and bewilderment, and in severe cases the patient may give the impression of being in a dazed and mildly confused condition.

The dysphoria, which is the constant affective disturbance, is of quite a distintictive type, and differs from both that of dysoxia and neurotic depression. There is never the tense and anxious misery of the neurotic, or the dull and bewildered perplexity of the typical dysoxic, or the agitated and fearful state of the benign dysoxic or paranoid patient. The general impression on examination is that of a mild degree of depression, with a certain amount of resigned apathy and blunting of the normal emotional responses ; indeed, some of these patients do actually complain that they have lost the power of emotion and cannot feel as they should do normally. Many give the impression that their feeling-tone has become, as it were, frozen up within them.

The third symptom, cephalic paræsthesia, is also very constant and characteristic. It is described by means of expressions such as the following ; " there is something wrong inside my head," " my brain is not working properly," or " my head feels numb and empty." There is always complaint of great diffi-

culty in thinking clearly and poverty of mental imagery, although objectively there is no evidence of retardation and poverty of ideation of the usual dysoxic type. It should be emphasized that this form of cerebral paræsthesia is definitely not the same as the pressure-headache of the neurotic depressive, nor is it interpreted by the patient in the bizarre manner of the dysoxic or dysglycic subject.

Suicidal attempts, often of a determined nature, are not at all uncommon in this form of dysoxic disease.

At first sight, the derealization-depersonalization syndrome would appear to be more closely related to the neurotic depressions than to the true dysoxias, especially in view of the absence of the signs of projection and dissociation. The points of dissimilarity between the two conditions, however, are sufficiently great to show that they are not related, while the marked sensitivity of the syndrome to anoxia is a definite indication that it should be included among the dysoxic group of brain-diseases. Anatomically and pathologically, the condition may be considered to be a form of dysoxia in which the dysoxic process is localized chiefly in the higher thalamic centres and cortico-thalamic connections, the association-tracts and cortical cells at the highest cerebral levels being relatively unaffected. Such a pathology would explain adequately the sensorial and emotional anomalies together with the absence of the sensory and thought-disorders found in the typical dysoxias.

The course and prognosis of the derealization-states depend largely on the treatment given. In civilian practice, it is usually found that such conditions tend to run a rather chronic course of several months to a year or more when untreated by anoxia, although ultimately the tendency is towards spontaneous improvement. The acute form seen in military practice has usually a good prognosis ; many show a dramatic improvement after a single application of electroanoxia, and the condition may clear up entirely after three or four treatments. Unlike the ordinary forms of dysoxia, there appears to be little tendency to relapse. The more chronic cases, however, are sometimes much more obstinate, and may require the full course of 8 to 10 convulsions to effect remission.

The treatment of choice is, as already indicated, electroanoxia. Derealization-patients are singularly refractory to sedation, while benzedrine does not seem to affect either the depression or the unreality-symptoms—another fact which indicates the essentially

metabolic nature of these conditions. The very distressing nature of the symptoms and the long course of the disorder when untreated are definite indications for a radical form of therapy.

The differential diagnosis of the derealization-states will be evident from the very distinctive clinical features described above. The conditions for which it is most likely to be mistaken are the acute neurotic depressions and the benign form of dysoxia.

The former conditions are distinguished by the pronounced anxiety and hysterical features and absence of the characteristic feeling of unreality. The dysphoria and headache of neurotic depression are of a different type to that of the derealization-syndrome, and the combination of mental deficiency with the dysphoric features, so common in hysterical conditions, is practically never seen in the depersonalization states.

Benign dysoxia is readily distinguished by the delusions of guilt, agitation, retardation, aural hallucinations, and bradyphrenia. The disorder of thinking described by derealization-patients never attains the profound degree of psychomotor slowing seen in dysoxic depression of the ordinary type, and is rather a subjective feeling of being unable to think clearly and concentrate.

The following cases are illustrative examples of the derealization-depersonalization syndrome :—

Case 23. A private, aged 31, was admitted with a history of having developed an acute dysphoric state with anxiety and unreality-features while serving in Italy. He had a history of a similar depressive breakdown in civilian life several years previously. On admission, he was co-operative and sensible, but mildly depressed, puzzled, and bewildered in manner. He complained of a constant feeling of " being in a trance " and being completely unable to " snap out of it." His emotional reaction was one of mild depression and apathy. Physical findings were negative. He showed the typical derealization-syndrome, the unreality-features being referred both to himself and to the outside world. No relief was obtained from either bromide in large doses or benzedrine. He was accordingly given a course of electroanoxia, with immediate improvement, a total of six convulsions being given. On discharge he was much improved, although the derealization-symptoms persisted in mild form up to the time of discharge.

Case 24. A leading-aircraftman, aged 32, was admitted from a home-station with a four months' history of severe depression, feelings of unreality, and obsessive ideas of having pulmonary tuberculosis, of which he had always had a morbid fear. When first seen, he was acutely depressed, tense, preoccupied, and extremely puzzled and bewildered in his manner. He was rational and co-operative and showed no evidence of being retarded; his main subjective complaints were of a severe degree of unreality-sensations, inability to think clearly, impaired memory, generalized pains, and morbid fears of tuberculosis. No relief was obtained from benzedrine in full doses, but following the inception of electroanoxia, he showed a prompt response, and his derealization symptoms cleared up rapidly and completely after seven applications. He was finally discharged to his home in a state of remission.

Case 25. A leading-aircraftman, aged 24. Eight months previously, while serving in Italy, he had sustained a fractured femur and ulna in a motor-accident. Soon after repatriation and while under orthopædic treatment at a general hospital, he developed a severe depressive breakdown and attempted suicide by drinking lysol. On admission, he was rational and sensible, but obviously depressed and mildly apathetic. There was no evidence of retardation or other signs of typical dysoxia. His main complaint was of severe depression, feelings of unreality, extreme difficulty in thinking, and a peculiar feeling in his head, which he described as "feeling as if his brain had stopped working, and there was something wrong inside the head." He showed a mild degree of anxiety, with fears of insanity and of having sustained organic brain-damage as the result of his injury. There was no history of concussion, and typical post-concussive symptoms were not in evidence. No relief was obtained from bromide and benzedrine in large doses. His symptoms responded promptly to electroanoxia, and cleared up after four applications, assisted by reassurance and a simple explanation of the mechanism of anxiety and obsessional fears. His only residual symptom was a mild degree of difficulty in thinking, and he remained well up to the date of his discharge.

These three cases are quite typical of the derealization-depersonalization form of atypical dysoxia. They each show the characteristic combination of symptoms described above, namely, dysphoria, unreality-feelings, cephalic paræsthesia, and difficulty

in thinking, with absence of projection-symptoms, and the typical dysoxic response to electroanoxia. Case 25 differs in a slight degree from the other two, in that an element of anxiety and obsessional thinking was found in association with the unreality-features.

(4) Obsessive-Ruminative States

Before leaving the subject of the quasi-neurotic dysoxic states, there is one other condition akin to the derealization-syndrome which must be included in the dysoxic group of metabolic disorders. The group of conditions commonly termed the obsessional neuroses includes certain cases which, like the derealization-states and typical dysoxias, show the specific therapeutic response to anoxia, and hence must be discussed in connection with this group of conditions.

The obsessional states have been shown by several writers to have certain points of similarity to the encephalopathies, the most striking of which are the constitutional nature of the conditions, their gradual onset, and evolution over the same age-period, and the persistent autochthonous ideas and compulsive actions. It should be understood that this group includes only the chronic obsessional states of slow onset ; the venereophobic syndrome and injustice-neurosis described in a later chapter are acute forms of mixed anxiety and obsessional conditions, arising as a result of external stress. These conditions have an altogether different course and prognosis, do not respond to neurometabolic therapy, and are not included in this group of conditions.

Chronic obsessional conditions are not common in military practice, since most patients whose symptoms are obvious and very incapacitating are rarely passed as fit for service, while the milder cases quite frequently make a fairly good adjustment to service life ; this is not uncommonly the case, especially if they find their niche in duties of a type requiring meticulous care and attention to detail—for instance, clerical and administrative work—which, at the same time, does not impose too much responsibility on the individual. The obsessional individual, however, is always liable to break down and develop a severe anxiety-depressive reaction if brought up against duties which require much responsibility or initiative.

The type of obsessional case which is found to react most favourably to anoxia is the form in which the principal symptoms

are of the obsessive-ruminative type, with persistent unpleasant and distressing thoughts, associated with severe depression with or without feelings of unreality. The compulsive forms do not respond well to anoxia, and hence cannot be included in the dysoxic group of disorders. The following is a good example of the anoxia-sensitive type of obsessional case :—

CASE 26. A private, aged 19, was admitted from a home-station, with a history of over two years of obsessive symptoms of a gross type. He was passed fit for service by the recruiting medical board and broke down within a few weeks of joining his unit. He was an overdependent, shy and mother-fixated type of lad, with a slightly effeminate manner and way of speaking, and was handicapped by having a domineering, narrow-minded mother, who showed very little sympathy and understanding of his troubles. When first seen, he was rational and co-operative, but very tense and depressed. His main complaint was persistent obsessive thoughts of an obscene type, centring on God, religion, and his relationship with his mother, and of obscene words and phrases referring to his mother constantly intruding themselves into his mind. His conscious life was so completely dominated by obsessive rumination of this kind as to practically incapacitate him completely for all normal activities. He showed a mild degree of derealization, but true hallucinosis and other projection-symptoms were absent, and he showed good insight. The exhibition of benzedrine failed to produce any amelioration of his depression or effect upon his obsessional ruminations and capacity for normal activity. Accordingly he was given a course of nine applications of electroanoxia, with slow but progressive improvement and he was finally discharged to his home completely relieved of his obsessional symptoms.

The striking anoxic response in a case which would ordinarily be considered to be one of pure psychoneurosis is the remarkable feature in this case. Whether such a remission in a case of this type is likely to be lasting, however, is extremely uncertain, since the constitutionally obsessional nature of these patients remains fundamentally unchanged by any form of neurometabolic therapy, so that it would be expected that any undue emotional stress experienced subsequently would be very liable to produce a relapse. This type of case is that which would be expected to

derive most benefit from the operation of leucotomy, as described in a later chapter.

(5) Pseudo-Dysglycic Dysoxias

The affective response of elation and euphoria has already been referred to as one of the hallmarks of the dysglycic state, and one of the cardinal signs which distinguish it from the dysoxic reactions. There are, however, certain atypical forms of dysoxia in which the emotional reaction of euphoria is found in association with a typical dysoxic response to neurometabolic therapy. For this form the term pseudo-dysglycic dysoxia is suggested. Its characteristic features consist of elation and overactivity in association with a marked degree of underlying psychic tension in the form of explosive irritability, querulousness, and strongly appropriate and well-preserved affective responses. The manic and sensory forms of encephalopathy both furnish examples of this type. The diagnosis of this type of atypical dysoxia rests upon the presence of elation in association with a degree of marked inner tension, together with the apparently paradoxical non-response to hypoglycæmia and favourable response to anoxia. The following two cases are illustrative examples of this rather uncommon type of encephalopathy :—

Case 27. A private, aged 38, was admitted to the psychiatric ward from a general hospital, to which he had been admitted the day before complaining of abdominal pains. Within a few hours of admission to the surgical ward, he had started to exhibit gross delusional features with excitement and disordered conduct, necessitating his immediate transfer to a psychiatric hospital. On admission, he was co-operative and correctly oriented, but grossly deluded. He expressed numerous bizarre ideas that a gang of men were following him around with the intention of murdering him, that he knew all the plans for the invasion and conquest of Japan, and that he knew of various plots by spies and enemy agents. He was hallucinated by voices speaking to him and threatening him. His emotional reaction was of manic type, with marked elation, euphoria, and pressure of talk and activity, and he was abusive, agressive, and hostile in manner, with marked explosive irritability, impulsive outbursts, and periodic explosions of obscene language. Physical examination, blood Kahn test, and CSF findings were negative. As

he showed no evidence of spontaneous improvement, insulin therapy was tried, without the slightest mental improvement. He reacted at once to a course of electroanoxia, however, and following this was considerably improved, became much quieter and more tractable, and, although remaining excitable and paranoid in general outlook, his gross sensory features faded considerably into the background. Intelligence tests showed him to be a high-grade mental defective.

This case is an example of the atypical form of sensory pseudo-dysglycic dysoxia. The emotional reaction, delusions of fantastic type, and hallucinosis were of apparently typical dysglycic form, but the paradoxical neurometabolic response shows that the case was undoubtedly a true dysoxia. The querulous and irritable type of affective response also shows that the underlying disorder was undoubtedly dysoxic in type.

CASE 28. A private, aged 38, with a record of 11 years' regular service. He had a history of always having been backward, with a poor school-record. He was admitted with a history of having recently become excitable, overactive, and talkative, with deterioration of conduct and repeated absence without leave. When admitted, he was garrulous, elated, euphoric, and distractible, with a typical manic flight of ideas and marked emotional ability. He showed partial insight, was correctly oriented, and hallucinosis and sensory phenomena were absent. Physical examination, blood Kahn test, and C.S.F. were all negative. As no spontaneous improvement was apparent, he was given a course of electroanoxia totalling six applications, with a good response and final remission. He was eventually invalided and discharged to his home in a state of remission.

This case is a good example of the manic type of pseudo-dysglycic dysoxia. The euphoria and overactivity would at first sight appear to stamp this case as one of simple dysglycia, but the rapid response to anoxia and well-preserved emotional responses show that the patient was a true dysoxic case. The misleading nature of the symptomatology and the value of the neurometabolic response as a diagnostic test is again illustrated in these two cases.

CHAPTER VIII

DIAGNOSIS FROM ORGANIC CONDITIONS

The diagnosis of the metabolic encephalopathies from the "organic" reaction types may sometimes present a difficult problem. Of the two main types, dysoxia is the most likely to present diagnostic difficulties, since there is a number of organic states which may produce an acute confusional symptomatology closely resembling that of the dysoxic syndrome. Acute dysglycia, on the other hand, has a symptomatology so peculiar and characteristic that it is unlikely to be mistaken for any other condition by a careful observer. The principal form of dysglycia which may present difficulties is the acutely excited confusional form.

The principal common non-metabolic conditions from which the metabolic encephalopathies may have to be distinguished are the "organic states," and the gross forms of hysterical, anxiety, and psychopathic states. The latter conditions will be fully discussed in the next chapter, while for the present the organic conditions alone will be considered. Of these latter the common ones which may simulate acute dysoxia are acute and chronic infections of the nervous system, epileptic states, cerebral tumours, poisons, and disorders secondary to organic disease of other organs, of which uræmia is a good example.

(1) General Paresis

Syphilis of the central nervous system deserves special mention, since, both in military and civilian practice, it seems to have developed a predilection for the younger age-groups in recent years. Its onset is not uncommonly in the 30 to 40 age-group, and cases occurring in the 25 to 30 age-groups are not unknown, these last being possibly of the late congenital type. Moreover, the exalted grandiose type described in the text-books appears to be less common now, while the simple dementing type is comparatively common.

In the latter form the early symptoms may bear a very strong resemblance to an early dysoxic state. The physical signs often

described in text-books, such as Argyll-Robertson pupils, intellectual impairment, and motor signs, are very often completely absent or only very slightly marked in the early stages. In the writer's experience, they are totally unreliable for diagnostic purposes, since pupillary abnormalities, muscular tremors, and epileptiform phenomena are not uncommon in the acute phases of some types of metabolic encephalopathy. The excited grandiose form is most likely to be mistaken for an acute dysglycic excitement, as illustrated by the following case :—

CASE 29. A gunner, aged 31, was admitted with a history of recent onset of elation, grandiose religious ideas, and noisy and threatening behaviour. On admission, he was noisy and excited, resistive and maniacal, and exhibited destructiveness and faulty habits. He expressed grandiose delusions of wealth and of religious type. This condition alternated with periods of querulous weeping and emotional outbursts, with a vaguely paranoid outlook, but hallucinations were not in evidence. His flow of speech was rambling and disjointed, but memory and orientation were unaffected. C.N.S. signs were negative apart from slight labial tremor, slurring of speech, and mask-like facial expression. The blood Kahn test was strongly positive, and the C.S.F. findings typically paretic. There was no history of lues, but exploration of his family history revealed that his mother had had one miscarriage and one stillbirth prior to the birth of the patient.

In this case the acute mental symptoms, with intact intellectual powers and very slight C.N.S. signs might easily have led to the diagnosis of an acute dysglycic state ; since the mask-like facies with absence of expression and slight tremors are not uncommonly found also in the acute encephalopathies. The absence of hallucinations in combination with grandiose delusions and elation is, however, not common in typical acute dysglycia and this sign should always lead to a suspicion of the correct diagnosis in these cases.

The simple forms of paresis are most likely to be mistaken for a subacute dysoxic reaction. In the early stages, the gradual onset of apathy, with dullness, mild depression, loss of interest, and occasional mild ideas of reference, may be very suggestive of the former disorder. Intellectual impairment of any degree is very often conspicuous by its absence in the early stages of

evolution of the disorder, and this serves still further to confuse the diagnosis.

In the writer's experience, the two earliest and most reliable signs in early paresis are the peculiar ironing out of the facial expression and the alteration in the voice, the characteristic monotony and slight slurring of speech becoming noticeable in the very early stages. The investigation of the serological reactions in the blood and cerebro-spinal flood in cases where there is any doubt should always settle the diagnosis. It has been the writer's practice to do routine blood Kahn tests in all cases where there is any element of doubt, and C.S.F. tests in addition to these where any suspicious signs or history of syphilis are present.

The following case is a good example of how general paresis of the simple type may simulate malignant dysoxia :—

> Case 30. A regimental sergeant-major, aged 31, with a record of 17 years' excellent service, was admitted with a history of recent onset of progressive apathy, loss of efficiency and bed-wetting ; his admission followed an acute amnesic episode in which he had made three attempts to find his way back to his unit from on leave, but each time had become completely lost. The area-psychiatrist who first saw him had made a provisional diagnosis of " schizophrenia." His relatives stated that for the last few months he had been becoming apathetic and disinterested, and had developed the habit of bed-wetting. On admission, he was dull, apathetic and solitary with a lethargic manner, vacant expressionless facies, disorientation for time, and impairment of recent memory. He displayed no insight for his condition, expressed no spontaneous complaints, and said he felt that there was nothing whatever wrong with him. Examination of the C.N.S. was completely negative, the only unusual physical feature being a mild pyrexia a day or so after admission. The blood Kahn test was strongly positive, and the C.S.F. findings of typical paretic type. There was no history of previous syphilis. He made an excellent response to induced malaria and arseno-bismuth therapy, and was returned to duty in full remission.

This case illustrates very well how easily an organic condition can simulate a dysoxic depression, the unreliability of C.N.S. signs in such cases, and how serological tests may be the only clues to the diagnosis.

(2) The Parkinsonian Syndrome

Occasional cases of the post-encephalic syndrome occur in military practice ; they are usually very mild and chronic cases, who have been passed fit for military service by the recruiting-board without their disability being detected.

The fixed expression, apparent dullness, bradyphrenia and bradykinesia, with poverty of emotional expression, apathy, and often depression of mood and fleeting ideas of reference may produce a clinical picture which strongly resembles the malignant forms of dysoxia ; the more so, since in mild post-encephalitics the characteristic tremors, rigidity, and salivation may be absent, and there is usually no history of an acute attack in the past.

The most reliable signs in the writer's experience are slight inequality of the pupils, defective convergence, poverty of vocal expression and a negative blood Kahn with normal C.S.F.

The following case, in which a mixture of hysterical and quasi-dysoxic signs were prominent, is a good example :—

Case 31. An airman, aged 31, with two years' home service. He had no previous history of *encephalitis lethargica*. He was admitted with a history of difficulty in vision six months previously, followed three months later by paræsthesias and feelings of numbness in the left side of his face and body, nausea, head-ache, difficulty in walking, and transient periods of mental confusion lasting a few hours at a time. He had been under investigation in a general hospital as a case of suspected cerebral aneurysm, but had to be transferred to the psychiatric ward, as he had become extremely depressed and mentally confused, the diagnosis of mixed schizoid and hysterical state having been made prior to his transfer. On admission he was dull, depressed, mentally confused and apathetic,with ideas of reference and fleeting aural hallucinations. His main complaints were of head-ache, general weakness, and acute depression. He showed a typically Parkinsonian mask, with fixed stare and expressionless features, general attitude of slight flexion, unequal pupils, slight right external rectus weakness and defective convergence. General slowness of movement, lack of initiative and motor anergia were marked, but tremors, rigidity and sialorrhœa were absent. The blood Kahn, C.S.F., and radiogram of the skull were negative.

(3) Epileptic States

The type of constitutional cerebral dysrhythmia which is most likely to be mistaken for the metabolic disorders is that which is characterized by periodic episodes of mental confusion, excitement, conduct abnormalities and hallucinosis, in which convulsive phenomena are absent. The acutely excited type with hallucinosis is most likely to be mistaken for malignant dysglycia, while the dull, confused, and amnesic type is more likely to simulate the dysoxic states. Such epileptic states are not uncommon in military practice; in some cases, the man may have a previously normal history, the acute episode having a sudden and abrupt onset following exposure to severe battle-stress. Moreover, a history of "fits" in combination with a negative electroencephalogram should not be taken as necessarily diagnostic of epilepsy, since peculiar epileptiform attacks occur sometimes in the encephalopathies, due apparently to an acute autonomic disturbance. The diagnostic difficulties may be considerably increased if electroencephalography is not available.

The principal clinical features to look for in the differentiation of an epileptic state are the periodic occurrence of the psychic episodes with intervening periods of normality and the occurrence of features atypical in metabolic encephalopathy. Such features are, for example, katatonia in combination with convulsive phenomena, a poor response to neurometabolic therapy with favourable response to anticonvulsant drugs, and evidence of epileptic rather than schizoid or cyclothymic temperament. The electroencephalogram is, of course, the most reliable diagnostic test, and in combination with any of the above features, an abnormal E.E.G. should confirm the diagnosis of an epileptic condition.

(4) Mental Deficiency

Amentia in its milder forms, with or without neurotic symptoms or behaviour-disorder, is most likely to simulate the malignant forms of dysoxia.

It not infrequently happens that the psychiatrist is called upon to examine and report upon a man who is stated by his superiors to be dull, stupid, slovenly in habits, and unable to assimilate the simplest military training. In cases of this type,

the dullness, childish and facile manner, apathy and general slovenliness found in defectives of this kind may bear a very strong resemblance clinically to the state of affairs seen in the malignant dysoxias. Intellectual tests are not always of help in these cases, since in both conditions the results obtained may be vitiated by apathy and inattention of the patient, genuine or otherwise.

The previous history of the man may be of valuable assistance in dealing with these cases. In the case of aments, the dullness and backwardness dates from an early age ; the most common history is that the patient has only reached a low standard at school, has lived at home with his parents most of his life, and has never been able to aspire to any occupation other than simple labouring jobs. In simple dysoxics, however, careful examination may reveal that the condition has been an insidious degenerative change of gradual evolution in a previously more or less normal individual. In the dysoxic, there may or may not be evidence of mannerisms, fleeting delusions of reference and hallucinations, periods of transient confusion, or impulsive episodes. A history of dullness and apathy in combination with repeated disciplinary offences is, generally speaking, much more typical of simple dysoxia than of amentia. The presence of hysterical and anxiety concomitants is almost diagnostic of simple mental deficiency, as such reactions are often developed by the defective as part of his general inferiority-situation ; whereas the simple dysoxic is characteristically apathetic, lacking in sense of shame, and quite unable to appreciate the consequences of his actions owing to disorder of judgment and insight.

In some mental defectives, whose backwardness has resulted in their being bullied, teased, and generally made the butt of all their comrades, paranoid ideas with a setting of depression and anxiety not uncommonly develop, and this condition often superficially resembles in its clinical features the paranoid form of dysoxia—especially since in the severer forms the degree of depression may be extreme and not uncommonly a determined suicidal attempt may occur. In these cases, the patient's complaints are commonly those of being victimized, laughed at, talked about, and generally badly treated by his comrades or N.C.O.'s. The paranoid ideas, however, usually have a strong factual basis, and never assume the bizarre symptomatology of the true dysoxic. Hallucinosis, confusion, autochthonous ideas, and feelings of passivity are absent, and the pseudo-paranoid

features clear up rapidly and spontaneously within a few days of the patient's removal from his unit to the hospital. This type of neurotic reaction will be further discussed in the chapter on acute neurotic depression and its diagnosis.

(5) Traumatic Encephalopathies

Head-injuries occurring under military conditions may, as in civilian practice, be followed by acute encephalopathic reactions strongly resembling, if not identical with, the dysoxic and dysglycic states. Thus, within a few hours or days of the injury, the patient may pass abruptly into a clouded state, with excitement, paranoid ideas, hallucinosis, and conduct-disorder, with or without evidence of intellectual damage. The following case is an illustrative example :—

> Case 32. A sapper, aged 27, sustained a head-injury with concussion and fracture of the left radius and ulna while on active service in France. He was admitted to a general hospital for orthopædic treatment, and while there developed an acute encephalopathy of dysglycic type. When admitted to the psychiatric award, he was elated, euphoric, noisy, aggressive, and resistive. Orientation and memory were defective, and he showed the usual anterograde and retrograde amnesia for the circumstances attending his injury. He was grossly deluded, and stated in response to questioning that he was a squadron-leader in the R.A.F., had shot down 18 rocket-bombs in combat, and had received his injuries while making a dive-bombing attack on a V2 site. He also expressed bizarre somatic delusions that his left eye and the muscles of his left leg had come out. This condition showed no signs of spontaneous improvement, and hypoglycæmia was accordingly started. His response was rapid, and he made a complete recovery with insight. On discharge, he showed no evidence of intellectual damage, and the only abnormal sign in the C.N.S. was a left-sided diplopia. A radiogram of the skull was negative, and his previous history showed no evidence of neuropathic instability.

This case would appear at first sight to have been one of acute dysglycia precipitated by cerebral trauma, with, possibly, a fractured base. In spite of the prompt response to hypoglyglycæmia, the patient's normal pre-encephalopathic history, C.N.S. signs, and confusional-confabulatory features would appear

to indicate that this case was one of true post-traumatic rather than typical metabolic encephalopathy. The absence of characteristic dysglycic hallucinosis in combination with the delusional features is another atypical sign, which is not found as a rule in the typical acute dysglycic states.

The following case is an example of a post-traumatic condition simulating malignant dysoxia :—

Case 33. A gunner, aged 27, was invalided from Italy following a gunshot wound in the head, received while in action on the Burma front in February, 1944. On admission he was in a state of passive stupor, and completely mute, inaccessible, and without interest in his surroundings. Katatonic signs were absent ; physical examination showed a small scar and healed depressed fracture of the temporal bone just behind the left ear and immediately above the external auditory meatus, but there was no evidence of abnormal localizing signs in the C.N.S. The stuporose features responded readily to amytal narcoanalysis, he became accessible, talked quite sensibly, and was able to give quite a good account of himself, but was very childish and facile in manner. The stupor returned as soon as the effect of the barbiturate had worn off. During the lucid period, the patient admitted having had aural hallucinations and bizarre paræsthesias while in his stuporose phase. A few days following analysis, he had a typical hysterical fit. As the stuporose signs showed no evidence of spontaneous resolution and were unaffected by benzedrine in large doses, he was given a course of electroanoxia, which was followed by marked improvement. Following six applications, the stupor cleared up completely, and although facile, childish, and simple in manner and showing a moderate degree of post-traumatic dementia, he remained co-operative and well-behaved with freedom from hallucinosis and hysterical features up to the time of his discharge.

In this case the history, physical findings, and evidence of organic dementia undoubtedly point to a post-traumatic syndrome rather than a primarily metabolic type of disorder ; the hallucinosis and rapid response to electroanoxia, however, would indicate that an element of dysoxia was present, while the hysterical signs would indicate an admixture of motor hysteria. The evident difficulty in classifying this type of case and deciding whether it is a purely organic condition due to cerebral trauma or

predominantly a metabolic encephalopathy is well illustrated by these two cases.

It would appear to be most logical to regard atypical conditions of this sort as mixed states, in which a metabolic disorder is superimposed on a brain already organically damaged, and to assume that a cerebral trauma of this kind can, in addition to causing organic brain-damage, initiate an acute cerebral metabolic upset. This would account for the good response to anoxic and hypoglycæmic therapy which is sometimes seen in these cases, as also for the bizarre and typically encephalopathic symptomatology often encountered, such as hallucinosis and delusions.

It is not uncommonly found that patients who have recovered from an acute encephalopathy often give a history of head injury some years previously, to which they often attribute their breakdown; in not a few such cases there is a history of a recent cephalic trauma, without evidence of post-concussional symptoms or brain-damage, immediately preceding the metabolic breakdown. In the writer's opinion, in the first group of cases, the cerebral trauma can be discounted as a precipitating factor, unless definite residual nervous signs are evident; while in the second group, the head-injury can most probably be considered to be a definite precipitating factor of the metabolic breakdown.

(6) Toxic States and Poisons

The conditions commonly described in the older text-books by such terms as "toxic confusional insanity," acute delirious mania, collapse delirium, or infective-exhaustion psychosis may be considered to be simply hyperacute forms of the dysoxic-dysglycic syndrome, in which the precipitant factor is an acute infection or other such toxæmia. The course and prognosis are similar to those of the acute malignant forms of dysglycia and dysoxia. The acute toxic encephalopathies cannot be considered to be distinct and separate entities from the former conditions, since they often progress to a typical dysglycic state, both in military and civilian cases. This variety of encephalopathy would include the puerperal and post-febrile forms seen in civil practice.

With regard to the alcoholic encephalopathies, there is little difficulty in differentiating the form with Korssakoff's syndrome and intellectual degeneration. The hallucinatory-paranoid types

without dementia are indistinguishable from the ordinary paranoid dysoxias as regards their course and neurometabolic response, while delirium tremens may be regarded as a special form of acute dysglycia. The same remarks apply in the case of the encephalopathies found in narcotic addiction, such as cocaine-paranoia.

Acute cannabis and mescaline intoxication, as already described, are toxic conditions which can simulate exactly the acute dysoxic and dysglycic states. They are not common on this side of the Atlantic, and may be differentiated by the history of drug-taking, and in the case of mescalism, by the very characteristic pupillary changes.

In general practice, the only common drug-dyscrasia which may simulate metabolic encephalopathy is chronic bromide-intoxication, a condition to which increasing attention has been drawn by several writers in recent years. It is uncommon in military practice, as would be expected. Chronic bromism may give rise to a variety of acute and chronic mental syndromes, such as depression, lassitude, and bradyphrenia, which may simulate a mild dysoxic state ; acute confusional and excited states, which may simulate the acute dysoxic and dysglycic reactions, and acute maniacal encephalopathies simulating the simple form of dysglycia. The diagnosis rests upon the history of prolonged bromide-medication, the presence of cutaneous eruptions, the characteristic sweetish odour of the breath, and the estimation of the bromide content of the blood. Of general metabolic disorders, those likely to offer difficulty are insulin-intoxication, diabetes mellitus, uræmia and hypertensive states, and arteriopathic disorders with mental symptoms.

Insulin-intoxication in diabetics due to an accidental overdose may produce an acute state of maniacal or confusional excitement which may strongly resemble an acute dysglycic episode. The diagnosis may be puzzling if the patient, as sometimes happens, is picked up in the street in this condition and carrying no indication that he is an insulin-treated diabetic. The diagnostic points are the abrupt onset of the excitement, the presence of other signs of insulin-poisoning, such as sweating, tremors, and salivation, and the therapeutic effect of glucose administration. The estimation of the blood-sugar is diagnostic.

Chronic diabetes, in which the main symptoms are those of depression lassitude, and general deterioration of efficiency, may resemble somewhat the early stages of a dysoxic depression.

The hunger, loss of weight, and examination of the urine and blood-sugar in these cases are the diagnostic tests.

Uræmic and hypertensive encephalopathy may give rise to acute confusional or excited states which may simulate a dysoxic or dysglycic reaction. Examination of the cardiovascular system, urine, and blood-urea, and, in arteriosclerotic patients, the age, usually give the clues to the correct diagnosis. Arteriosclerotic encephalopathy of the type in which the symptoms are predominantly mental is not likely to be confused with the metabolic states, on account of their later age of onset and the intellectual changes commonly found.

(7) Cerebral Tumours

The only type of cerebral neoplasm which is likely to present a clinical picture similar to those of the encephalopathies is the slowly-growing frontal type with no localizing signs and symptoms principally in the psychic sphere. In the early stages, the apathy, emotional changes, and general mental deterioration may offer a clinical picture which is practically indistinguishable from dysoxia of the simple type. Diagnostic pointers are combinations of atypical symptoms, such as katatonia with convulsive phenomena —a feature which is never seen in the metabolic states. Slight changes in the optic discs, sensory astereognosis, and, in cases where the growth is cortical or subcortical, the electroencephalogram, may confirm the diagnosis.

(8) Acute Infections of the Nervous System

Encephalitis epidemica in its acute stage may simulate a dysoxic state, when it occurs in the form characterized by dullness, apathy, general depression, and mental confusion. The form with acute excitement, delirium, overactivity, and pressure of talk, may simulate acute dysglycic excitement. The diagnosis may be difficult in sporadic cases, especially in cases where cranial palsies and other characteristic C.N.S. signs and febrile symptoms are absent or very slightly marked.

Suggestive features are the absence of aural hallucinosis and ideas of reference, and the presence of pyrexia. In all doubtful cases, the examination of the C.S.F. for cells and increased protein should assist in the diagnosis.

Cerebrospinal meningitis commencing with an acute delirium may occasionally simulate exactly an acute dysglycia, especially in cases where the C.N.S. signs are very slight or absent, and the mental symptoms render the patient uncooperative to detailed examination. The writer has seen at least two cases of fulminating meningitis with delirium admitted to the psychiatric ward with the diagnosis of "acute mania." In the absence of an epidemic, the diagnosis may quite easily be missed in such cases, since pyrexia and extreme toxæmia are common in the fulminating dysglycias. In all doubtful cases, lumbar puncture should be performed as early as possible, if necessary under morphine and hyoscine in full dosage. The same remarks apply to tubercular meningitis, of which the following case is a good example :—

CASE 34. A private, aged 44, was admitted from a camp reception station with the history of having complained for the last few days of headache, nausea, and a bad taste in his mouth. When first seen at the C.R.S., he showed little abnormality apart from a mild pyrexia and rather toxic appearance. Within a few days of admission to the C.R.S. he became confused, excited, and dirty in habits, his general condition rapidly deteriorated, and admission to the psychiatric ward became necessary. On admission, he was acutely excited, restless, maniacal, and faulty in habits. He was agressive and abusive, with a generally hostile and paranoid outlook, and rambling and disjointed in speech. His behaviour suggested the presence of aural hallucinations. Physically, he showed no definite abnormality in the C.N.S. and other systems, but his general condition was poor, with evidence of recent loss of weight and some degree of toxæmia, but no temperature. Proper physical examination was impossible on account of his mental symptoms, which appeared to be those of a typical acute dysglycic state. He remained in this state for three days ; on the fourth he collapsed suddenly, and became deeply comatose with stertorous respiration, suffused features, and acute retention of urine. The pupils were unequal, and all reflexes diminished. The urine was highly coloured with a few cells and casts, the blood urea 44 mgms., and the Kahn test negative. His temperature and pulse-rate rose steadily, the pyrexia reaching 105 degrees. A lumbar puncture revealed fluid under moderate pressure, turbid, with a yellow tinge. The cells were markedly increased, 90 per cent. being lymphocytes, and the chlorides and

glucose greatly diminished. Culture was sterile. The patient's general condition deteriorated rapidly, death occurring in coma four days after admission.

This case was undoubtedly one of fulminating tubercular meningitis, commencing with purely mental symptoms, and imitating perfectly an acute dysglycic state, the true nature of the condition not being suspected until three days after admission, when the signs of an acute cerebral infection suddenly became manifest.

CHAPTER IX

DIFFERENTIAL DIAGNOSIS FROM NEUROTIC AND PSYCHOPATHIC STATES

(1) General considerations

The problem of the diagnosis of metabolic encephalopathy from neurotic states raises the much debated question of whether a sharp distinction can actually be drawn between them, or whether, as some workers assert, the grosser types of neurotic and personality disorders shade over indistinguishably into encephalopathy, and borderline states which might be assigned to either group of conditions occur. Undoubtedly conditions which appear to partake of the characteristics of both disorders are found, and not infrequently cases which commence as apparently purely neurotic reactions can evolve finally into a true encephalopathy. It is the writer's opinion that a definite line of distinction does indeed exist, and in this connection certain distinguishing features between the neurotic personality disorders and the encephalopathies will now be briefly discussed, before the actual diagnostic features of the various clinical syndromes is considered in detail.

Metabolic encephalopathy, as already shown, is an organic disorder due to deranged oxygen-glucose metabolism of the cerebral cells. The clinical and experimental evidence for this has already been set forth in detail in an earlier chapter. The neurotic states, on the other hand, are essentially emotional disturbances in which the signs of an organic disorder are absent, the primary disturbance being either an unresolved mental conflict or an upset of the autonomic functions, or a combination of both.

The encephalopathies are distinguished by one outstanding symptom which they all have in common and which is not found in the psycho-neuroses. This is a characteristic disorder of the sensory functions, as a result of which there is a gross disturbance of the normal relation between the self and the external world of reality. This is seen in the dysoxias principally as a disturbance

of the thalamic centres and affective functions, resulting in causeless depression, mental confusion, hallucinosis, and delusional ideas. In the dysglycias, it is seen principally as a disturbance of the sensory and associational centres, with characteristic ideational disorder, distortion and misinterpretation of perceptual stimuli, delusions and hallucinosis. In other words, there is in encephalopathy an osmosis between the real and the unreal, which shows itself in its most characteristic form in the symptom of projection, in which the patient's symptoms are ascribed to outside influences, a feature which is not seen in the neuroses. This disturbance is due to the metabolic disorder of the thalamic and cortical centres and their connections, and the same mechanism is found in the experimentally induced mescaline encephalopathy. Indeed, the encephalopathic might aptly be compared to an experimental subject who has received a dose of mescaline, and the neurotic to one who has received an overdose of some powerful autonomic stimulant, such as adrenaline or carbaminoylcholine. Thus, in the encephalopathic we have a total disturbance of the whole personality, which shows itself in the reality-disturbance and projection symptoms, and a profound affective disturbance which may be in the direction of incongruity, euphoria, or ecstasy as well as depression. The reality-disturbance is also seen in such gross conduct disorders as wetting and soiling in a setting of clear consciousness, destructiveness, and outbursts, and gross motor disorders at the highest level, as exemplified by the katatonic dysoxias. In the psychoneuroses, on the other hand, there is no such gross disturbance of personality and relation to reality, both of which remain well preserved throughout, and the gross motor signs and conduct-disorders do not occur.

In the sphere of thought, the gross disturbance of association and ideation of the encephalopathic patient is never seen in the neurotic states.

The affective disturbance in the neurotic differs fundamentally from that of the encephalopathic. The characteristics of the encephalopathic type of affective disorder have been indicated above ; in the neurotic however, the disturbance is essentially a simple dysphoria, in other words, the condition takes the form of of an abnormally lowered perceptual threshold for all unpleasant sensations and affects, with a correspondingly raised threshold for all pleasant affects and sensations. This symptom is common to all the neurotic states, and may occur either in manifest and generalised form, or it may be localised and disguised. In

the former type the patient may state frankly that he feels depressed, nervous, and in a state of general unpleasant mental tension ; in the disguised or conversion form, the symptom may present itself as a persistent headache, dyspepsia, or other unpleasant sensation without organic basis. Euphoria and emotional incongruity are never seen, nor is conduct affected in the gross degree seen in the encephalopathies. Neurotic dysphoria is also relieved temporarily by narcotic and euphoriant drugs, whereas the dysoxic form is either unaffected or made worse thereby. This is well illustrated by the fact that by far the greatest proportion of alcoholics and drug-addicts are recruited from the ranks of the neurotic and psychopathic, whereas addiction in association with metabolic encephalopathy is exceptionally rare. Thus, the administration of opiates over a long period to dysoxic depressives does not produce addiction, a fact which was made use of in the old-fashoined treatment of dysoxic depression with tincture of opium. This is an additional piece of evidence that the central nervous metabolism differs qualitatively in encephalopathics from that of normal and neurotic persons.

The type of personality-disorder also differs in the neurotic from that of the encephalopathic. In the case of the grosser hysterical states, the fragmentation of personality is molar, as seen in the acute amnesic fugue-states, whereas in encephalopathy it is molecular, as exemplified by the dementing forms of malignant dysglycia. In the hysteric, the process is temporary and recoverable, while persistent hysterical and anxiety-patterns are not accompanied by mental deterioration ; in the untreated encephalopathic, however, permanent dementia with organic changes in the brain and other organs can be demonstrated in a high proportion of cases.

In the intellectual sphere, judgment and insight are never grossly impaired in the neurotic as they are in the encephalopathic subject. This is one of the differentiating signs upon which especial stress is laid by most authors, and which generally speaking holds good, although slight qualification is sometimes necessary, as will be indicated in a later section of this chapter.

The sensory phenomena of neurotics differ also fundamentally from those of encephalopathics, in that they are never interpreted in the bizarre manner found in the latter condition, nor do they affect the patient's conduct in the manner seen in the encephalopathic. Complex aural hallucinations in a setting of clear consciousness are never found in neurotics, but are abso-

lutely characteristic of both the dysoxic and dysglycic states. Pseudo-hallucinosis and hypnagogic hallucinosis are seen in cases of hysterical dissociation, but they occur in a setting of clouded consciousness and are never interpreted in the bizarre encephalopathic manner. As previously stressed, it is not so much the sensory phenomena themselves as the way in which they are interpreted which has the most important diagnostic significance.

The response to narcoanalysis differs in the two conditions, as will be described in a later section. But most important of all is the response to neurometabolic therapy; in psychoneurotic states both anoxic and hypoglycæmia are ineffective as curative measures, whereas they are highly effective in cases of early encephalopathy, and in some of the atypical borderline conditions may constitute the only reliable diagnostic test.

The diagnosis of dysoxia from the acute anxiety and hysterical conditions is one of the most difficult clinical problems both in military and civilian psychiatric practice. Its importance need hardly be stressed, since the treatment of the two conditions is radically different, as is the prognosis when untreated. The acute hysterical and depressive anxiety states furnish a very large proportion of psychiatric war-casualties, both military and civilian; as they most commonly present themselves in the form of either an acute confusional or depressed state, it is evident that the condition from which they most often have to be differentiated is dysoxia, since they are unlikely to be easily mistaken for the dysglycic states, on account of the characteristically bizarre and peculiar symptomatology of the latter group of disorders.

Acute hysteria of the conversion or anxiety type, anxiety-states, reactive depressions, and certain obsessional and psychopathic personality-disorders may conveniently be considered together; they all belong to the group of personality-disorders which consist essentially of a severe emotional upset, without evidence of organic or cerebral metabolic disease, and they all have certain symptoms in common, of which the most characteristic is an acute depressive state.

Motor hysteria of the grosser type with paralyses and sensory anomalies of the classical type need not be considered here, as it is unlikely to simulate any of the metabolic disorders. Much more common in military practice are the acute affective forms of neurosis and the amnesic confusional states. These will now be considered together, as mixed forms not infrequently occur,

while the atypical psychopathic states will be considered separately in a later section. A brief description of the main clinical features will first be presented, followed by a detailed discussion of the differential diagnosis of the acutely depressed or confused patient as seen in war-time psychiatry.

(2) Acute Neurotic Depression

The clinical syndrome of acute neurotic depression consists essentially of a severe dysphoric affective reaction, associated with anxiety and hysterical features. It has a similar age-incidence to the acute dysoxias, and like them commonly occurs as a reaction to severe stress, such as prolonged exposure to enemy-action, although it also not infrequently occurs as a response to prolonged mental stress. It is the commonest form of " battle-neurosis " or " combat-fatigue." As with the metabolic disorders, constitutional neuropathic instability and mild degrees of mental defect are commonly associated, although, as in the case of the encephalopathies, cases not infrequently occur in men of sound previous personality and family history.

The clinical picture is very striking and characteristic. The patient presents a tense, drawn, and woebegone appearance, very often showing the fixed parkinson-like facial expression already described as occurring in the acute dysoxic states. The conjunctivæ are often injected, and the eyes have a moist and watery appearance, as if from prolonged weeping. Volitional and motor activity are usually greatly diminished, and the affective reaction is one of acute depression with marked tension and apprehension ; severe and distressing headache of diffuse and symmetrical pressure-type is a common complaint. Speech is low, halting, and monosyllabic, with marked hesitation and often severe dysarthria. The patient is often so tense and preoccupied as to give the impression of profound retardation and emotional poverty. Somatic anxiety-signs, such as sweating, generalized muscular tremors, vertigo, and acute vasomotor attacks are the rule, but gross sensory and motor anomalies of the cruder hysterical type are exceptional. A varying degree of amnesia and disorientation is a frequent finding.

In some cases, the dazed and apathetic state just described may be replaced by acute restlessness with signs of a severe panic-reaction associated with insomnia, nightmares, impulsive outbursts, and the startle-reaction recently described as a charac-

teristic symptom of the acute battle-exhaustion forms. In the form which occurs in psychopathic personalities of the aggresive type, there is often a marked degree of sullenness, suspicion, and hostility, which gives a strong impression of deliberate conscious exaggeration and malingering.

The degree of depression varies from a mild dysphoria with anxiety and tension to complete stupor with mutism and inaccessibility.

(3) Hysterical Confusional States

The hysterical confusional state has often an acute onset as a sudden fugue with massive amnesia, in which the patient may wander away from his unit and be picked up wandering aimlessly in a dull disoriented state. In other cases, the acute fugue may be preceded by a period of several weeks of increasing tension, anxiety, and depression. In the acute combat-fatigue type, the onset may be an attack of acute excitement with impulsive and violent behaviour, and, as with the depressive form, an impulsive suicidal attempt in the initial stages is not uncommon.

On examination, the patient presents the features of a dull, profoundly disoriented state, and is often completely mute and inaccessible. He may be completely unable to respond to questions, or may simply reiterate a phrase or sentence. Mask-like facies, tremors, and other gross anxiety and hysterical stigmata may be present. The patient usually tends to lie curled up or stretched out in bed, staring vacantly before him. In other cases, he may be tense, agitated, and restless, with marked somatic anxiety-signs. As with the depressive type, there may be evidence of a considerable degree of exaggeration and over-dramatization of the symptoms. Gross motor symptoms may be present in the form of astasia-abasias, tremors, paralyses, dysarthria, and often peculiar puffing and blowing noises when the patient attempts to speak, which may be so marked as to render his speech completely unintelligible. The peculiar mask-like expression, as already described for acute neurotic depression, may also be a feature observed in the confusional form. Impulsive outbursts and suicidal attempts are sometimes found, especially in cases with a psychopathic background and in patients of the depressed and inadequate type.

The above description is that of the acute amnesic form, as distinct from the affective type. Mixed forms frequently occur,

in which a combination of affective and confusional features is seen. The two types described above are those which commonly occur as a reaction to acute battle-stress, and for which the term "exhaustion-state" rather than "hysteria" is now commonly employed. Which one of the terms is used is of little account, since all these conditions are a form of acute emotional upset occurring as a reaction to severe mental or physical stress.

(4) Diagnosis from the Dysoxic States

The diagnosis of the confusional form has to be made from the malignant type of dysoxia. It will be evident from a consideration of the symptomatology described above that this may be a matter of extreme difficulty, since a profound degree of mental confusion and dissociation has the effect of masking to a great extent the accompanying symptoms, such as hallucinosis and ideas of self-reproach, which are the characteristic features of the metabolic disorder. The diagnosis of dysoxia from hysterical confusional states will be considered first.

In a case of suspected dysoxia, the features to look for are recurrent nocturnal restlessness, incontinence, destructiveness, and degraded habits, aural hallucinosis, ideas of reference, and delusions of self-reproach. Katatonic signs may be present if the case is one of dysoxia, but their absence is not a reliable diagnostic sign, as the case may be one of the simple or confusional type without characteristic motor phenomena.

The stupor of hysteria is of simple passive type, and mannerisms, stereotypy, waxy flexibility, and other dysoxic stigmata are not present. Severe sleeplessness and nocturnal restlessness are not as a rule marked, in contrast to what is found in dysoxia. Negativism, incontinence, and refusal of food are also absent, and the hysterical patient shows a much greater degree of suggestibility than does the dysoxic. Thus, a sudden call to pay-parade or the weekly cigarette-issue in a military hospital often has a remarkable and dramatic effect in temporarily abolishing the stupor and other hysterical symptoms.

The type of mental confusion in many cases of dysoxia differs strikingly from that of acute hysteria. Massive amnesia and disorientation may, of course, occur in both conditions, but is more characteristic of the hysterical fugue-state. The type of reaction in dysoxia, on the other hand, is more often a dull, perplexed, and apathetic state, rather than a true disorientation

in time and space ; the disorientation and memory-defect is very often more apparent than real, on account of the perplexity, bradyphrenia, and loss of contact with reality. Careful examination in such cases usually shows the memory and intellectual functions to be remarkably intact when the degree of apathy and perplexity is taken into consideration.

Hysterical, unlike dysoxic, confusion, shows a marked tendency to clear up spontaneously, often within a day or two of admission to hospital. A confusional state which persists for more than three days without evidence of spontaneous improvement is always much more likely to be dysoxic than hysterical.

The presence of acute headache, somatic anxiety signs, functional paralysis, amaurosis, or other sensory anomalies, indicates that the case is much more likely to be hysterical than dysoxic.

Finally, the response to narcoanalysis will in most cases nearly always decide the diagnosis in a doubtful case. In hysterical confusion, the result almost always is a complete and lasting resolution of the confusional features, while in dysoxia it is temporary, and the stupor and confusion return as soon as the effect of the drug has worn off. During the lucid interval so induced, the hysteric will talk sensibly and show a typical abreaction, whereas the dysoxic, although accessible as a result of the injection, may show evidence of fatuousness, irrelevancy, and hallucinosis in his talk, and there is never the strong degree of abreaction found in the hysterical patient.

The diagnosis of dysoxia from the affective form of neurosis is a more complicated matter, on account of the pleomorphism and extraordinary variety of the mental symptoms shown in this disorder. Dysphoria is probably the commonest single symptom in war-time psychiatric casualties, and the diagnosis of the acutely depressed patient is often one of very great difficulty.

In acute neurotic states, true hallucinosis of the complex aural and visual type, delusions, incontinence of urine and faeces in a clear setting of consciousness, and gross conduct-disorders, are absent, in contrast to what is seen in the dysoxic states.

Special mention should be made of the first symptom in this connection. In acute neurotic states, particularly those of the battle-exhaustion type, vivid nightmares with realistic dream-states and hypnagogic hallucinations are found, the content of which consists largely of the patient's battle experiences. These

symptoms have to be carefully distinguished from the true hallucinosis which is found in encephalopathics. One of the commonest mistakes made by the inexperienced examiner is in diagnosing and interpreting these symptoms as " hallucinations," and labelling the patient with the diagnosis of metabolic encephalopathy. The term " neurotic pseudohallucinosis " should correctly be applied to this symptom. In the same manner, anxious and depressed patients frequently complain of the simple type of auditory hallucinosis, commonly described by such terms as " noises in the head," " buzzing in the ears," and so on. These sensations, like the hypnagogic phenomena, are never interpreted by the patients in the bizarre manner seen in dysoxics.

In dysoxia, the patient's previous history is often good and the disorder is of sudden onset ; a long history of psychopathic tendencies and general maladjustment which culminates finally in an acute confusional or depressive breakdown is much more characteristic of neurotic depression. In neurotic depressives an obvious precipitating cause in the form of psychological stress is more common, while dysoxic breakdowns frequently have an acute onset with no apparent cause.

On the sensory side, acute headache of the pressure type, symmetrical, diffuse, and associated with severe tension and distress is typical of neurotic depressions. The same applies to gastric and other paræsthesias of classically hysterically type ; true hallucinosis associated with ideas of reference and persecution are, as already stated, found in dysoxia but not in neurotic depressive states.

On the motor side, functional paralyses, dysarthria, tics and tremors are almost always associated with neurotic depressive states ; katatonic rigidity, mannerisms, stereotypy, impulsive outbursts, incontinence and degraded habits on the other hand are found in dysoxia but not in neurotic depression. With regard to excitement and impulsive episodes, it should be mentioned that these sometimes occur as part of the panic-reaction in some forms of acute hysterical depression, especially of the battle-exhaustion type and in cases with marked psychopathic trends, but they are not accompanied by hallucinosis, habit disorders and the other dysoxic stigmata.

The physical examination may sometimes be helpful. The signs of toxæmia are commonly found in acute dysoxia, but are usually slight or absent in the hysterical, confusional and depressional states. Gross somatic signs of anxiety, such as sweat-

ing, tremors, and disorders of the cardiac rhythm, are on the other hand more commonly associated with the neurotic depressive states.

The subject of mental confusion and intellectual disorders has already been referred to in the section on diagnosis of the hysterical confusional states. The question of insight and judgment as diagnostic criteria will be discussed separately in a later section of this chapter.

The dysphoria of neurotic depression usually presents striking and characteristic features. It is strongly appropriate, shows a marked day-to-day variation, and is readily influenced by external factors, such as suggestion, environment, visits of relatives, and the promise of release on medical grounds from the service. It shows a much greater degree of inner tension, irritability, and anxiety, unlike that of the dysoxic patient. In neurotic depression there is often a noticeable degree of conscious exaggeration and dramatization, as with the other symptoms. In cases with psychopathic traits especially, there is a marked degree of sullenness and conscious malingering, as is commonly found in the confusional form. The neurotic depressive tends to blame others and his environment for his condition, and does not show the ideas of guilt and self-depreciation which are so characteristic of the dysoxic.

Dysoxic depression, in contrast to this, presents much more frequently the characteristics of a dull and perplexed state, with little evidence of anxiety and inner tension. Emotional incongruity and flattening are often present, and the depressive emotional reaction may alternate with periods of fatuous smiling and laughing. Conscious exaggeration is absent, and ideas of self-reproach and guilt centring round sex-matters, such as autoerotism, are common. The dysoxic, in contrast to the neurotic, tends to blame himself; very commonly such patients reiterate that there is nothing wrong with them, that they should not be in hospital at all, and should be returned to their unit for a court-martial and duty. This is in striking contrast to the querulous, aggrieved attitude of neurotic depressives, in whom the sense of injustice and unfair treatment is often so characteristic. Further reference to this feature in the diagnosis will be made later in connection with the condition of obsessional "injustice-neurosis."

In cases of dysphoria in which severe tension and agitation rather than apathy and dejection are the prominent features,

diagnosis in the early stages is often difficult, since neurotic depression of the acute exhaustion-type may present features which closely simulate those of agitated dysoxia. For example, such a case may show the symptoms of acute confusion and disorientation, panic-reactions, disconnection and incoherence of thought, impulsive episodes, and suicidal tendencies. The diagnosis of these cases rests on the absence of true dysoxic signs, such as hallucinosis, delusions, incontinence, and so on, and their tendency to spontaneous improvement with or without sedation and narcoanalysis, and their characteristic poor response to electroanoxia.

This last feature is extremely important; as previously stressed, anoxia is specific for dysoxic but not for neurotic depression, and the latter condition almost always shows a negative response to this form of therapy, as would be expected from theoretical considerations. The reason for this is undoubtedly that the effect of anoxia in dysoxic depression is due to reversal of the cerebral metabolic disturbance, whereas in neurotic depressions, which are due to an emotional conflict without metabolic upset, the underlying cause of the condition is not affected by the therapy. In the few neurotic dysphorias which do respond to anoxia, the effect is undoubtedly a non-specific one due to a sudden shock aided by powerful suggestion. In any case of "neurotic depression" which clears up rapidly under anoxia, while resistant to ordinary methods of therapy, the diagnosis should always be suspect; similarly any case of "dysoxic depression" which shows no response to anoxia is almost certainly an atypical hysterical or obsessional state. From these observations, it will be evident that electroanoxia may be used as a valuable diagnostic test in dysphoric states where the diagnosis is in doubt.

As with the confusional type, the response of the two conditions to narcoanalysis is also a valuable aid to diagnosis. Acute hysterical stupors and depressions can often be completely abolished by a single injection of amytal or pentothal, and do not recur, the patient being left with simply the usual anxiety and hysterical residua, such as tension, headaches, general nervousness, and mild depression. In dysoxic stupor, however, there is usually a dramatic but transient response, the patient relapsing quickly into his stuporose condition as soon as the effect of the drug has worn off. Again, as with the confusional

form, the strong abreaction of neurotic depression and hysterical states is asbent in the dysoxic patient.

Of vegetative disturbances, sleep-disorder in its severer forms is more often encountered in dysoxic states, especially when associated with restlessness and agitation. Many neurotic depressives sleep well in spite of their frequent assertions to the contrary; in neurosis, the patient usually finds difficulty in falling off to sleep during the early part of the night, but sleeps soundly when once asleep. In depressed dysoxics, however, waking up in the small hours of the morning with difficulty in getting off to sleep again and restlessness is more typical. This symptom is mentioned in most text-books as a fairly reliable diagnostic criterion, and the writer's observations have in the main confirmed this.

Symptoms referable to the gastro-intestinal tract frequently occur in both conditions, and may be valuable diagnostic signs. In neurotic depressions, functional dyspepsia, often of very chronic duration and associated with other hysterical symptoms, is a common finding. Anorexia with persistent complaints of obstinate constipation and progressive loss of weight are more typical of dysoxia, as are such features as fixed ideas of intestinal stoppage and dysfunction, which are commonly associated with delusions of bodily disease and a marked degree of persistent obsessive rumination. Bizarre paræsthesias referred to the gastro-intestinal tract may occur in hysterics as well as in dysoxics; the important difference, however, is not the symptom itself but the manner in which the patient interprets it, and whether or not it is projected.

Vertigo of non-organic type, a common symptom, is much more typical of the depressive neurotic with anxiety-symptoms. It is commonly described by such terms as "dizzy turns," giddiness, or a "swimming" feeling.

(5) The Suicidal Patient

Suicidal attempts occur frequently in both neurotic and dysoxic states, and a suicidal history, contrary to what is sometimes stated, is not necessarily diagnostic of dysoxia. In the writer's experience, genuine suicidal attempts occur about as frequently in severely depressed neurotics as often as they do in dysoxic patients. The nature of, and circumstances surrounding the attempt, may, however, be a useful guide to diagnosis.

A sudden and determined attempt, especially by taking poison, in a patient with a previously stable history, is more likely to be an early symptom of encephalopathy. This is particularly so when no definite precipitating cause, such as acute grief or unhappiness, can be elicited, and where the attempt takes place in solitary surroundings. In acute neurotic dysphoria, particularly of the battle-exhaustion type, there is usually much less evidence of deliberation, and the attempt is often sudden and impulsive ; nearly all self-inflicted injuries in men whose morale has given way temporarily under stress occur in this manner. It is indeed surprising how many depressed neurotics who, according to their own accounts, genuinely try to shoot themselves, manage to miss a vital part at zero range.

A history of several half-hearted and ineffectual attempts is much more characteristic of the chronic hysteric and psychopathic personality. On the other hand, a history of a past severe depressive illness associated with a determined suicidal attempt and subsequently followed by complete recovery is an almost certain indication that the illness in question was an acute dysoxic episode.

Threats of suicide are not usually found in true dysoxic cases, although many of these patients who have insight will often readily admit their preoccupation with suicidal ideas. Threatening suicide is much more characteristic of the hysteric and psychopath, and is a favourite device for gaining a desired end, which in military cases is nearly always discharge from the service.

As previously mentioned, sudden suicidal attempts are particularly common in the agitated paranoid type of dysoxia. In the case of a patient who presents marked tension with vague ideas of grievance and victimization without definite evidence of hallucinosis or other frankly dysoxic signs, one should always be very careful to exclude an early dysoxia before pronouncing the patient to be non-suicidal ; since, in these cases, the confusional episodes, hallucinosis, and typical dysoxic delusions may be completely absent in the early stages, and may only reveal themselves after several days of careful observation.

The attitude of the patient towards his suicidal attempt is sometimes a useful sign in diagnosis. Psychopaths and hysterics generally try to make the most of their troubles in order to gain sympathy and the desired end. Dysoxics, on the other hand, because of their affective disorder and lack of insight, tend rather to make light of their conduct-disorder and rationalize it accor-

dingly. Others, whose insight has not yet been too greatly impaired, realize the seriousness and possible repercussions of their symptoms and conduct, and so try to rationalize and cover it up as far as possible

The question of suicide and its diagnostic importance may be briefly summed up by stating that an acute dysphoria of recent onset which is accompanied by a genuine suicidal attempt in a man of previously stable personality-type should always be regarded as most probably part of an acute dysoxic breakdown until otherwise proved.

(6) Insight and Judgment

The above considerations raise the important question of the presence or absence of insight, in the diagnosis of neurotic depression from the dysoxias. The presence of insight has always been regarded as one of the classical distinctions between psychoneurosis and encephalopathy ; this is, of course, broadly speaking correct, but by no means invariably the case. In military practice, for instance, we see cases of early encephalopathy in which insight and judgment are to a large extent comparatively well preserved, while, on the other hand, cases of acute hysterical confusion and neurotic depression are not infrequently encountered in which contact with reality is so impaired as to produce disorder of insight and judgment of considerable degree. This is most commonly seen in the acute confusional forms of hysteria ; very often a patient in an acutely confused and perplexed state with absence of dysoxic features will assert that there is nothing the matter with him, and the same gross defect of insight may also be found, although less commonly, in some cases of the acute depressive type of neurosis.

In contrast to this, an early dysoxic of the more intelligent type may exhibit quite a marked degree of insight ; thus, he may complain that he feels strange and has abnormal sensations, and describe his hallucinations and ideas of reference as " ideas " or " imaginations." In the acute forms, of course, insight is always grossly impaired, on account of the widespread damage to the association-centres and their connections.

It will thus be evident that the presence or absence of insight alone is not necessarily always a reliable diagnostic feature, particularly in acute confusional states, and that lack of insight

alone should not be regarded as necessarily indicative of a dysoxic state, if other clinical features of this condition are absent.

(7) Special Forms of Neurotic Depression

In addition to the depressive and confusional forms of acute neurosis just described, there are three other forms which have become increasingly common during the course of this war. They are considered together because they all belong to the class of acute obsessional states, and exhibit in common the cardinal symptom of a fixed idea. These conditions are the Injustice Neurosis, the Venereophobic Syndrome, and the Marital Infidelity Syndrome. All three are extremely frequently mistaken for the paranoid form of dysoxia.

(*a*) "Injustice Neurosis." This term is used by the writer to describe a type of case encountered quite commonly in military and civilian practice. Brief reference has already been made to this condition as being particularly liable to occur in feeble-minded individuals, hysterical personalities, and psychopaths of the aggressive and cantankerous type, when they are faced with the problem of adaptation to military conditions and discipline. A common and typical case-history is as follows:—

The patient, usually a mental defective or psychopath, who has managed to make a fair adaptation in civilian life, finds that in his unit his clumsiness, low intelligence, and general ineptitude make him the butt of his comrades and N.C.O.'s; he is bullied, teased, and laughed at, and is constantly in trouble on account of disciplinary offences. As a result, he develops a paranoid attitude, culminating finally in an acute dysphoric breakdown.

On admission, the patient is tense, anxious, acutely depressed, querulous, and persecuted in outlook. He dwells constantly on his grievances and injustices; complains that he "is not wanted," is being "victimized by all and sundry," and his life is made intolerable by teasing and chaffing by his comrades. He complains that N.C.O.'s "pick on him," and "take the mike out of him." In the case of aggressive psychopaths, impulsive outbursts and assaults are not uncommon, and suicidal attempts are not uncommonly found. In the case of mental defectives and inadequate personalities, the patient is often acutely depressed and miserable, and a generally disgruntled, hostile and suspicious attitude towards authority in general is the rule. Multiple hysterical pains and anxiety-signs are a usual finding.

It is evident that this condition may easily be mistaken for the paranoid type of dysoxia on superficial examination, and the salient diagnostic features are the following. In the true injustice-neurosis, delusions of persecution, autochthonous ideas, hallucinosis, and confusional features are absent. The ideas of persecution have always a strong basis of fact, and are referable solely to the unit in which the man has been serving. They and the other symptoms invariably clear up spontaneously within a few days of the patient's removal to hospital, and the prognosis is always good—that is to say, there is no tendency to the development of dysoxic features. Indeed, many of these cases are in fact precipitated as the result of harsh treatment and lack of understanding.

The salient points in this form of neurosis are the fixed ideas of injustice and resentment, accompanied by marked anxiety and hysterical symptoms, and the condition should be correctly classed among the obsessional states. As would be expected, it responds to psychotherapy and general measures, and is completely refractory to electroanoxia.

(*b*) The Venereophobic Syndrome. This peculiar form of obsessional state has come into increasing prominence recently, largely as a result of the increase in the incidence of venereal infection and the sensational publicity campaign to which the public has been subjected recently in connection with these diseases. The type of personality in which it most commonly occurs is the anxious, overscrupulous, and rigid type, usually of rather over-average intelligence. The typical case-history is as follows :—

A man of the type just described becomes anxious and worried either as the result of exposure to infection or hearing a lecture on V.D. and its fearful consequences when untreated. On admission, he is acutely anxious, tense, emotional, and depressed ; he complains of headache, multiple pains without organic basis, and generalized paræsthesias of anxiety-type. His main topic is a fixed idea that he has contracted venereal disease, and the sensory symptoms are always ascribed to this. This idea is completely refractory to reassurance and persuasion, and the man has usually had a series of negative blood-tests from several venereologists without in the least affecting his obsession. Marked feelings of guilt and self-reproach are often present.

The acute tension and dysphoria with feeling of guilt and *idée fixe* amounting practically to delusional force give the

condition a strong superficial resemblance to an acute dysoxic depression. As in the injustice-neurosis, however, true hallucinosis, delusions of persecution, confusional episodes, and bizarre features are absent; there is no true projection, and there is nothing inherently absurd or fantastic in the patient's belief that he may have an undiagnosed venereal infection. As is the case with other similar conditions, the venereophobic syndrome is entirely refractory to electroanoxia and hypoglycæmia, and is, indeed, extremely refractory to any form of therapy. The prognosis is, however, always good, and the condition shows a marked tendency to spontaneous remission.

(*c*) The Marital Infidelity Syndrome. This is the third type of depressive-obsessional state, in which anxiety-symptoms are associated with a fixed idea. In this form, the patient, usually a man of the worrying inadequate or jealous paranoid type, develops the idea that his wife is unfaithful, and in consequence develops a severe emotional upset of neurotic depressive type. The condition often occurs in men who have been serving overseas for long periods, with consequent enforced separation from their wives and families, but it is also seen quite commonly in civilian practice. The typical case-history is usually as follows:—

A man who has been serving for several years in an overseas theatre receives a letter, either from his wife or anonymously from a neighbour informing him that she has been unfaithful to him. In other cases, the patient begins to believe that his wife has been unfaithful on only the flimsiest of evidence, such as talk among other men in his unit on the subject of marital difficulties and domestic worries in general. In other cases, failure to receive any mail from home for a long period is the precipitating factor. The patient gradually becomes more anxious and depressed, and in these cases a suicidal attempt is not uncommon.

On examination, the patient is tense, anxious, and depressed, exhibiting all the usual features of an acute anxiety-depressive state. He is entirely preoccupied with the idea that his wife has been unfaithful and with his suspicions about her, and this idea is entirely impervious to argument and persuasion; an interview with the wife and relatives nearly always proves that the patient's suspicions are unfounded, but in spite of this, his fixed idea persists. Anoxic therapy is as ineffective in influencing it as are psychotherapeutic methods. The ultimate prognosis is nevertheless good, and the condition tends to resolve spontan-

eously in the course of a few weeks. As with the two other obsessional states described, no form of active therapy appears to have any effect upon its course, apart from the assurance that he will eventually obtain his discharge on medical grounds from the service.

As with the previous two conditions, the marital infidelity syndrome is distinguished by the absence of confusion, hallucinosis, ideas of passivity, and other dysoxic features, the patient being perfectly rational and displaying good insight and judgment in all matters other than his fixed obsession. As with the venereophobic syndrome, there is nothing inherently absurd or fantastic in the patient's fixed idea, especially when the present social conditions created by the war are considered, and in many infidelity-cases the obsession is found to have a strong basis of fact. The negative response to anoxia is additional evidence for a non-dysoxic basis for this form of depressive state.

(8) Personality Disorders and Psychopathic States

Psychopathic personality has become increasingly prominent as a clinical syndrome in wartime psychiatry, and often presents a bizarre and bewildering combination of symptoms, which may show a strong resemblance to those of the true metabolic encephalopathies. The principal symptoms which are common to both the constitutional psychopath and the encephalopathic are states of depression, excitement, mental confusion, and conduct-disorders.

In many psychopaths, there is a history of delinquency, poor work and school-record, conduct-disorder, and criminal tendencies dating from an early age; whereas in encephalopathy the history is almost always that of the onset of a recent personality-change in a previously normal and reasonably well-adjusted individual. In some cases of psychopathy, however, the previous history may be negative, the individual having possessed sufficient stability to adapt fairly well to the conditions of civilian life, the underlying emotional instability having only become apparent following exposure to the unwonted stresses imposed by military service-conditions. Moreover, in many undoubted cases of psychopathy there may occur a superimposed encephalopathy, which is often complicated by the admixture of gross hysterical and anxiety-symptoms which further tends to bscure the true nature of the condition. This type will be more

fully discussed in a subsequent chapter under the term of hysteroencephalopathy.

Psychopathic personality may be conveniently divided into the excitable-aggressive type, in which most of the cases with delinquency and conduct-disorder are found, and the emotionally inadequate type, in which states of dysphoria strongly resembling the dysoxias are commonly encountered. The following case is a good example of the aggressive type of psychopathic reaction simulating acute dysglycia of the manic form :—

CASE 35. A gunner, aged 26, with four years' home-service, was admitted with a history of aggressive outbursts, uncontrollable temper, and alcoholic episodes, which rendered him a disturbing influence and general nuisance in his unit. He had previously been discharged from the army in 1937 on psychiatric grounds, and had a long history of emotional instability. His wife stated that for several months prior to hospitalization he had been " very queer " in manner. He had been diagnosed by the psychiatrist who first saw him as a case of hypomania. On admission, he was aggressive, disgruntled in attitude, rambling and disjointed in speech, and showed defective memory and orientation. He was facile and elated in manner, with defective judgment, and exaggerated ideas of his own importance and ability. He gave a poor account of himself, and tended to perseverate constantly in conversation. He exhibited a peculiar nervous tic of the right eye-muscles and lips, which resulted in an unpleasant leer and expression of low cunning. Physical examination was negative apart from a right inguinal hernia, and no abnormality was found in the C.N.S. His blood-Kahn test was negative. During his period of observation, he showed no evidence of hallucinosis or delusional activity, and his condition improved rapidly under rest and mild sedation. He was finally discharged from the service much improved. There was no evidence to suggest an epileptic basis for his condition.

The diagnostic points in this case were the previous history of chronic neuropathic instability without deterioration, the absence of delusional and hallucinatory features, and the rapid spontaneous improvement without the aid of neurometabolic therapy.

The following case is a good example of a psychopathic personality disorder simulating simple dysoxia of the malignant type :—

Case 36. A private, aged 21, home-service only, was admitted with a history of having become apathetic, slovenly, dirty in habits, and generally a bad influence in his unit. He had for the last few months been constantly in trouble for absence without leave and other petty disciplinary offences. His case-notes showed that he had previously been discharged from the army on psychiatric grounds in 1941. On admission, he was dull, detached, apathetic, and sullen in manner, with apparently a mild degree of disorientation and amnesia. He showed a marked degree of motor anergia, and lay passively curled up in bed betraying no evidence of interest in his surroundings. There was no evidence of hallucinosis or delusional activity, his habits were clean, and negativism was not in evidence. Physical examination and serological tests were negative. His mental symptoms cleared up completely within 24 hours of admission, and it was evident that there was a strong element of conscious malingering. He remained during the rest of his stay in hospital a whining, disgruntled, and paranoid individual, with poor morale and obvious desire to procure his discharge from the army. He was finally transferred to another military hospital, and maintained his improvement at the time of transfer.

The diagnostic points in this case were the past history, absence of projection and dissociation, and the rapid spontaneous resolution of the hysterical symptoms.

The following case is an illustrative example of an unusual type of personality disorder with hysterical features in a psychopath of the constitutionally inadequate type :—

Case 37. A private, aged 25, with negative previous history, was admitted with a history of conduct-peculiarities and failure to make a satisfactory readjustment following liberation from a prisoner-of-war camp in Germany, where he had been in captivity for five years. He had been provisionally diagnosed as " schizophrenia " by the area-psychiatrist, and was stated to be totally unreliable, simple and facile in manner, and generally useless in his unit. On admission, he was well-behaved and co-operative, but showed a moderate degree of emotional flattening and incongruity, diffuseness and irrelevance in thought, poor concentration, and a childish and simple manner. His complaints were of depression, feelings of unreality, difficulty in thinking, suicidal impulses, and general asthenia. He showed no evidence of hallucin-

atory or delusional actvity, nor were ideas of passivity in, evidence. Physical exaimination and serology were negative He improved spontaneously after a week or so in hospital. and was returned to his unit with a recommendation for interview with the personnel-selection officer. Within a week or so, he again commenced to exhibit conduct-abnormalities, necessitating readmission. He again improved following mild sedation, and was finally invalided as unfit for further service.

The final diagnosis in this case was hysterical personality-disorder in a man of poor personality-type, the diagnostic points against encephalopathy being the absence of projection and dissociation-features and the rapid spontaneous improvement.

(9) Malingering

The writer is in agreement with most service psychiatrists that pure and unadulterated " lead-swinging " is an extremely uncommon condition. As will be seen from the subject-matter of this chapter, however, it will be evident that a large conscious element of exaggeration and malingering is a frequent finding in hysterical and psychopathic patients. The writer has only seen two undoubted cases of pure malingering during the whole of his experience as an army psychiatrist, and careful examination of ncarly all cases diagnosed as malingerers always reveals a psychopathic history, hysterical trends, or a degree of mental defect. These are the three commonest conditions in which malingering may be found as a symptom.

It should be pointed out in this connection that recovered encephalopathics, when questioned about their breakdown, sometimes assert that they were simply malingering. This may be due to either lack of insight, conscious deception, or repression of the memory of the abnormal experiences. It is sometimes found in men of good morale and personality who realize the serious nature of their symptoms and try to rationalize and make light of them, in order to avoid discharge from the service on psychiatric grounds.

CHAPTER X

COURSE AND PROGNOSIS

Morbid processes in general may be considered to have two stages in their evolution—first the stage of activity, in which the pathological lesions are reversible and recoverable, with or without treatment, and second, the end-stage, or phase of quiescence, in which the active process has ceased, and the end-result in the form of permanent and irreversible structural damage alone remains.

From the clinical point of view, the outcome of any disease may be one of three possibilities—recovery with no residual damage, partial recovery with some residual damage, and death. The rule holds good for the metabolic encephalopathies, as for other pathological conditions, with the proviso that for death is substituted mental death, that is to say, permanent and irreversible dementia. In the early or acute stage of encephalopathy, the morbid metabolic changes may be reversible, and recovery, either spontaneous or assisted by neurometabolic therapy, may ensue. If, however, the disease is allowed to progress, permanent and irreversible changes may occur in the higher cerebral neurones and association-tracts. It is a fact well-known in general medicine that a primarily metabolic disorder is capable of producing permanent changes of a degenerative type in the various organs, if it is allowed to persist for a sufficiently long period of time Examples of this are the cardio-vascular changes produced as the result of long-standing diabetes mellitus or thyrotoxicosis, or the skeletal and adipose changes produced as the result of pituitary disease.

Of all the metabolic encephalopathies, the two conditions which are most likely to produce irreversible cerebral changes and dementia are the malignant dysoxias and dysglycias. Thus, the acute forms of malignant dysglycia often dement with extraordinary rapidity; whereas the benign forms of dysoxia, such as those of the involutional type, may remain for years in a state of profound apathy and depression only to make a dramatic and complete recovery with or without the aid of neurometabolic therapy. The reason for this is as yet unknown; we can only say

that the malignant forms of encephalopathy appear to be a much more destructive process to the personality than the benign types. It is probable that in the benign forms, the metabolic process is largely confined to the thalamic nuclei and their connections, the centres concerned chiefly with emotional activity. In the malignant forms, however, the most highly developed parts of the brain, the cortical neurones and association-tracts which are concerned with the highest form of intellectual and perceptual activities, are selected for attack, and, as in the case of other diseases, their powers of resistance and recovery are considerably less than those of the less highly developed and specialized centres located in the basal regions of the central nervous system.

An enormous amount of literature, supported by masses of carefully-compiled statistics, has accumulated in recent years dealing with the prognosis of the metabolic encephalopathies from the point of view of the aspects of heredity, type of symptomatology, pre-encephalopathic personality, somatic constitution, and so on. The writer's experience would indicate that one factor alone is of real importance—namely, the presence or otherwise of irreversible cerebral changes, in other words, the duration of the disease, and that, in comparison with this, other factors such as those outlined above are of comparatively minor importance. This is what would naturally be expected, since the longer the duration of the disease, the more likely will structural alterations of degenerative type have set in in the cerebral neurones and association-tracts. It may be here stated that, for all practical purposes, a case of encephalopathy of more than three months duration cannot be considered to be an "early case," and this applies particularly to the malignant dysoxias and dysglycias, the two forms of encephalopathy in which the destructive process and consequent dilapidation of personality are liable to be particularly rapid.

(1) General Prognostic Factors

Assuming that any given case is of less than three months' duration, the following factors do not necessarily indicate a poor prognosis; mental defect, the shut-in type of personality, bad heredity, an admixture of hysterical symptoms, and the presence of dyssymbole, which last sign will be more fully discussed in a subsequent part of this chapter.

A favourable prognosis is not necessarily indicated by the presence of the following factors; a good pre-encephalopathic

personality, a sound family-history, an acute onset with evidence of severe stress as the precipitating factor, and the presence of a strongly appropriate emotional reaction.

Of these factors, mental defect does not seem to influence the course of the disease unfavourably, contrary to what might be expected, It is a not uncommon finding in the acute dysoxias and hysterodysoxias, and many of the most dramatic remissions under electroanoxia occur in mental defectives, especially when the precipitating stresses, such as inability to adapt to the demands of service life, are at once removed by the admission of the patient to hospital and subsequent discharge from the service.

An acute and stormy onset is particularly common in the malignant forms of dysoxia and dysglycia, and in these cases it is not uncommon for the disease to progress rapidly even after the precipitating factors referred to above have been abolished. Not uncommonly this type of encephalopathy occurs suddenly in men of open and extroverted personality with a sound family and previous history, and these cases very often run a steadily downhill course with frequent relapses and progressive mental deterioration.

Special mention should be made here of the dyssymbole sign in dysoxia and dysglycia. Hitherto its presence has generally been regarded as an almost invariable indication of an unfavourable prognosis, but the writer's experience would indicate that this is by no means always the case. The sign may occur in the early stages of the disorder, and in these cases it is, like the other symptoms, reversible, and does not necessarily indicate the presence of irrecoverable cerebral changes. As seen in late cases, however, it is simply one of the indications of irreversible degenerative lesions in the higher association-centres. Good remissions without residual signs may be obtained in early cases of both types, even when the sign is demonstrably present in its florid form.

(2) Prognosis of Individual Clinical Syndromes

The prognosis in dysoxia varies according to the clinical type of the disease. The benign form has the most favourable outlook generally, and recovery, with or without the assistance of anoxic therapy is the rule in the great majority of cases. There is little or no tendency to dementia, unlike the malignant dysoxic and dysglycic forms, so that even very long-standing cases of the

involutional or chronic melancholic type may clear up with electro-anoxia. If there is a history of previous attacks with remissions, the probability is that this will again be the outcome. A benign dysoxia often clears up completely with the exhibition of two or three anoxic convulsions. These remarks are, of course, qualified by two additional factors, namely the possibility of suicide and the occurrence of dysoxic relapse at some later period. The latter possibility is always likely if there is a previous history of recurrent depressive attacks.

The principal peculiarity of the malignant form is not that it is refractory to specific therapy, but that it has such a marked tendency to relapse. Malignant dysoxia, both of the katatonic and confusional type, always shows the same dramatic response to anoxia as does the benign form, often with complete abolition of symptoms after five to seven anoxic convulsions, only to relapse completely within a week or so of ceasing treatment. To produce a lasting remission, three or four courses of electro-anoxia comprising a total of anything from 12 to 20 applications may be required. The possibility of permanent cerebral changes occurring in these cases is accordingly greater on account of the more prolonged course of the disorder. In the acute form usually encountered in military practice, the symptoms which are of specially ominous import are a profound degree of stupor or katatonia, strong feelings of guilt and self-reproach, repeated attacks of confusion, and an early age of onset.

The simple form with apathy and progressive blunting of interest and emotional response ("dementia præcox" of the older writers) has, on the whole, the least favourable prognosis, on account of its insidious onset and consequently late stage of evolution when first seen by the psychiatrist. In the early stages, however, the response to anoxia may be very good, and the prognosis therefore at least as favourable as in the katatonic and confusional forms.

In the hallucinatory-paranoid types the prognosis is, on the whole, good. The acute agitated form may require on an average nine to ten applications of anoxia to effect remission, and the tendency to relapse is much less marked than in the malignant types. A fact worthy of note is that often in the paranoid form no improvement is noted for the first five to six applications, and the hallucinosis and delusions appear during this period to be particularly stubborn and refractory to therapy. Improvement and finally remission then occur rather suddenly towards the

termination of the course. The course and prognosis of the alcoholic forms are similar, provided that there is no intellectual deterioration present.

The principal hazard in this form of dysoxia in the writer's experience is a sudden and determined attempt at suicide while under the influence of the distressing hallucinosis and ideas of reference. These patients sometimes show great cunning and determination in their attempts to obtain the wherewithal for suicide, and for this reason should always be under special observation during the acute phase of their disease.

The course and prognosis of the derealization and other atypical forms have already been indicated in the section dealing with these forms of dysoxia.

In dysglycia the same remarks apply generally as regards factors of heredity, family history, pre-encephalopathic personality, and duration of the disorder.

In malignant dysglycia, when untreated, the end-result is the same as in the corresponding form of dysoxia—namely, the chronic deteriorated and apathetic dement, the chronic disturbed refractory-ward case, or the wet, dirty, and degraded patient leading a purely vegetative existence. These types are familiar to all who have worked among the chronic mental hospital population. In contrast to the sensory forms, rapid and progressive destruction of the higher centres and personality-dilapidation is the general rule in untreated or late-treated cases. When diagnosed early and adequately treated by hypoglycæmia, however, a favourable outcome may be expected in the great majority of such cases, as in the relapsing type of dysoxia. Relapse, as in the case of the latter disorder, is always liable to occur, and in the present state of our knowledge of these conditions vigorous and adequate neurometabolic therapy appears to be the only safeguard.

The sensory or delusional forms differ from the malignant types in that, although the condition tends to be progressive when untreated, there is little or no tendency to personality-deterioration, so that the end-result is a comparatively well-preserved patient with chronic hallucinosis and fixed delusions. The rare systematized form (paranoia) has invariably a bad outlook, on account of its insidious onset and progress, so that by the time these cases are seen by the psychiatrist they are already in the late and established stage. At present it must be considered to be an incurable form of brain-disease, and its rarity

renders it of comparatively insignificant importance for the purposes of this work.

The outlook in the non-systematized form (paraphrenia, dementia paranoides, paranoid schizophrenia, etc.) is considerably more hopeful, provided the case is of recent onset. Those with a chronic history often respond well to hypoglycæmia with complete remission, only to relapse disappointingly within a few weeks or months of ceasing treatment. Case 14 is a good example of this type. The danger of rapid personality-deterioration, as already emphasized, is absent in this form, and a good result may be expected in cases of recent onset, provided that adequate and thorough hypoglycæmic therapy is given. Signs pointing to a poor prognosis in this type are fixed delusions and hallucinosis, apathy and affective deterioration, and a marked degree of regression as shown by the presence of bizarre symbolism, neologisms, and other dyssymbolic features; these, when uninfluenced by hypoglycæmia, are indications that irreversible changes have occurred in the higher association-neurones and their connections.

(3) The Course in Untreated Cases

All those who have worked in civilian mental hospitals will be only too familiar with that grotesque and pathetic figure, the chronic encephalopathic dement, the "faded lily," or "extinct volcano" type of patient, as the author has heard them graphically described. Such patients, the end-product of untreated metabolic encephalopathy, may be divided roughly into the following five categories:—

Firstly, the quiet, docile, apathetic, and mildly demented case who may be seen any time mechanically and assiduously polishing the floor of the hospital corridor, or being herded along in a drove by a uniformed attendant. These patients, although devoid of all initiative and normal interest, have still sufficient cortex and association-tracts functioning to enable them to lead a mechanical and routinized existence under supervision and sheltered surroundings. This type is usually the end-product of untreated malignant dysoxia or dysglycia, which has not progressed to complete cortical disorganization.

Secondly, we have the demented, wet, and dirty patient who leads an entirely vegetative existence and is completely helpless and dependent. These may be seen at any time lying in bed in

a side-room, sitting about the ward making a few grimaces or mannerisms, or simply just sitting. They are usually, like the first category, the end-products of the malignant encephalopathies, in which the metabolic process has progressed remorselessly and irreversibly damaged all or nearly all the neurones and association-tracts at the highest cortical and cortico-thalamic level.

Thirdly, the chronically excited, noisy, destructive, and violent cases who are permanent residents in the refractory ward. These patients serve to keep the artisan-staff busy replacing smashed window-panes and maintain the hospital drug-bill at constant level by their steady annual consumption of sulphonal and paraldehyde. This type is the final product of the katatonic dysoxias and alternating dysoxic-dysglycic forms, the aggressive delusional dysglycias, and dysglycias of the chronic manic type.

Fourthly, the chronically deluded patients, who may either be examples of the last-mentioned category, or of the extinct volcano type whose delusional ideas do not interfere with their working capacity as trusty working patients. These cases are usually examples of the chronic sensory-paranoid type of dysglycia.

Fifthly and lastly, the chronic depressed cases, especially those of the involutional type. This type should become much rarer with the advent of electroanoxic therapy, which has had its most striking successes in this type of dysoxic disease.

The course and mode of progress of a metabolic encephalopathy may aptly be compared to that of a forest-fire, the forest being the cerebral cortex and the trees its component neurones and association-tracts. As an unchecked forest-fire spreads in summer from tree to tree, burning down the trees and leaving only lifeless and charred stumps, so does the dysoxic or dysglycic process spread from one cortical region to another, leaving only burned-out neurones and fibres, their functions irreversibly damaged and impaired for ever. If the forest-fire is checked, only localized and reparable damage in the form of burnt-out patches of vegetation may remain, but if it progresses without hindrance, the result is finally a charred and lifeless waste. So, in the same way, in a case of metabolic encephalopathy recovery, total or partial, may occur with early and vigorous treatment ; if the disease is allowed to run on untreated, the end-result is the deteriorated and degraded dement, with his personality and higher intellectual functions hopelessly and irrecoverably damaged for ever.

(4) Post-encephalopathic Residua

A number of residual symptoms are often found persisting in some measure after the resolution of the active encephalopathy, whether or not specific therapy has been given. These may be severe and permanent, or of trifling and temporary nature. The former are the specific post-encephalopathic residua of organic type, due to degenerative neuronic changes, and the latter are simply non-specific after-effects of the type commonly found temporarily after any severe and debilitating illness, whether mental or physical, or after any terrible and shattering psychological experience ; these latter symptoms are, of course, purely exhaustion features, and clear up usually with rest and appropriate general measures.

Of the specific organic residua, the most commonly encountered are apathy of greater or lesser degree, emotional deterioration, lack of insight, intellectual impairment, and fixed and persistent hallucinosis and delusions, which are unaltered by any further neurometabolic therapy. Such cases may be compared to the post-encephalitic type of patient, and may subsequently make a limited social adaptation or finally require admission to a civil mental hospital, according to the severity or otherwise of the residual symptoms.

Of non-specific post-encephalopathic exhaustion-symptoms, the commonest are mild depression, aprosexia, insomnia, lack of self-confidence, asthenia, and minor degrees of anxiety and emotional instability. The knowledge itself of having had a mental breakdown, often precipitated by terrifying experiences, and of having been a patient in a mental hospital together with the associated torturing mental experiences, constitute a severe psychic trauma which often leaves its mark temporarily on the sufferer in the same way as any other unpleasant or terrifying ordeal. The prognosis of these temporary residua is generally good, their tendency being towards spontaneous resolution, and their therapy will be discussed in the chapter on after-care and treatment.

(5) Individual Symptoms and their Prognostic Significance

Although the type of symptomatology encountered in any given case is of much less importance as a prognostic guide than

the duration of the attack, there are certain symptoms which do afford a certain amount of information as to the probable outcome, and these will now be considered individually.

Mental confusion and disorientation are always to be looked upon as symptoms of ominous significance, contrary to what is commonly asserted by many writers at the present day. The reason for this is that by far the commonest syndrome with which this symptom is associated is the malignant form of dysoxia, and the presence of confusional features in a patient under thirty years of age should always be given a guarded prognosis for this reason. This statement holds good even in cases with a sound family and pre-encephalopathic history, and where the onset of the breakdown is an acute one following infection or exhaustion. Especially ominous is the form in which the encephalopathy takes the form of a dull, restless, and perplexed state with little or no evidence of positive features such as hallucinations and delusions, and katatonic features are absent. Recurring attacks of confusion, which show a good immediate response to anoxia with repeated relapse, are also a bad prognostic feature.

In acute dysglycic cases, the presence of mental confusion is of less significance, since it usually responds readily with the other symptoms to hypoglycæmia, the degree of response to this therapy and the presence or otherwise of signs of dysglycic deterioration being the most important prognostic features. In the sensory dysglycias, the occurrence of confusional features has the same prognostic significance as in the malignant form. Generally speaking, it may be said that in all forms of encephalopathy in which confusional symptoms are a prominent feature a marked tendency to relapse is almost always associated.

Apathy and emotional blunting are likewise symptoms especially associated with the simple form of dysoxia. Generally speaking, the prognosis in this form is bad if the case is one under twenty years of age, if the symptoms have been present for over six months, and if there is no evidence of positive features in the form of hallucinosis and delusions. Some cases of simple dysoxia, however, may do well on electroanoxia if the disease is still in its early stage and irreversible cortical changes have not yet occurred.

Affective incongruity, silliness, and emotional bizarreness in dysglycic cases which persists in spite of intensive and adequate hypoglycæmia are signs of organic damage to the thalamic and thalamo-frontal neuronic systems. They are especially of bad import when associated with an indifferent, offhand manner and

recurrent episodes of excitement and restlessness with persistent aural and somatic hallucinosis, autochthonous ideas and feelings of control. Other signs of dysglycic dementia are intellectual dilapidation in the form of irrelevance, disconnection of the stream of talk, and inability of the patient to describe his feelings.

Depression and increased intrapsychic tension are, as a general rule, favourable prognostic signs, particularly if they occur as a feature of the benign or paranoid dysoxic syndromes. However, when this symptom is associated with confusional features and katatonic signs, or occurs in a patient under the age of thirty years, it must be considered as indicating in all probability a malignant dysoxic reaction, and the prognosis should accordingly be guarded.

It should also be borne in mind that a severe anxiety reaction sometimes occurs as a secondary feature in the early stages of a malignant dysoxia or dysglycia, and the possibility of this being the underlying condition should always be excluded before making a prognosis.

Hallucinations and delusions are less important in themselves than the affective setting in which they occur and the other features with which they are associated. Persecutory delusions and hallucinations in a depressive setting are usually of favourable import unless associated with mental confusion and other features of malignant dysoxia. Bizarre delusions and hallucinosis which persist or recur repeatedly, usually in association with phases of confusion and excitement, in spite of adequate neurometabolic therapy, are of bad import. This is because such features are commonly found in malignant dysglycia with irreversible neuronic lesions. In dysoxia, the type of disease which has an ominous prognosis is that with a guilty or self-accusatory content, especially when associated with episodes of recurrent confusion and katatonic motor signs.

Acute excitement occurring for the first time in a patient under the age of 30 years is always a symptom of an acute dysglycic state, nearly always of the catastrophic type. Some cases, especially when associated with states of exhaustion and malnutrition as found in repatriated prisoners of war, may improve spontaneously and remit without special treatment. Recurrent attacks of excitement, especially when associated with typical dysglycic hallucinosis and feelings of passivity, are of bad import. It should be emphasised in this connection that an acute onset with adequate precipitating factors in a man of sound personality

does not necessarily mean a good prognosis if other dysglycic features are present.

Faulty habits, such as incontinence, destructiveness, and negativism are symptoms either of the acute dysoxic or dysglycic state, and are not necessarily of bad import unless they take the relapsing form.

The presence of anxiety and hysterical features in combination with a dysoxic breakdown is usually a favourable sign, since it indicates that the case is probably one of the hysterodysoxic syndrome, in which the prognosis is generally good. As previously mentioned, however, pure anxiety symptoms may also be found in the early stages of both dysoxia and dysglycia of the malignant form.

Stupor of the simple or passive type is usually found in benign and paranoid dysoxia, and usually indicates a good prognosis. If it is associated with perplexity, vagueness, restlessness, negativism or other katatonic signs, it indicates that the dysoxia is of the malignant type, and the prognosis in these cases should be guarded accordingly. Katatonic motor signs, such as rigidity and waxy flexibility, are always signs of the malignant dysoxic state and the prognosis is accordingly more serious, especially if there is evidence of marked feelings of guilt and self-reproach.

The dyssymbolic sign has already been referred to in connection with prognosis. As already stated, it is found in three conditions, namely malignant dysoxia, and malignant and paranoid dysglycia. When found in the early stages of the disorder, it is not necessarily a bad prognostic sign; when, however, it persists in spite of adequate therapy it is always indicative of an irreversible dysoxic or dysglycic lesion of the association-systems. Persistent evidence of intellectual deterioration, which is frequently associated with this sign, is similarly of bad prognostic import.

CHAPTER XI

THE SYNDROME OF HYSTEROENCEPHALOPATHY

Up to the present we have considered only the pure forms of metabolic encephalopathy and their differentiation from functional conditions of the hysterical and neurotic depressive type. There is, however, an important and fairly common group of cases in which the characteristic feature is the combination of a metabolic encephalopathy with hysterical and anxiety-symptoms. This condition is seen occasionally in civilian practice, but occurs in its most striking form in military cases, and constitutes a syndrome so peculiar in clinical features as to merit a separate and special description.

The condition has been noted previously by other workers, and the form encountered in military practice was described by the writer and given the name " hysteroencephalopathy " in an article originally published in the *Journal of Mental Science* in 1944. Since that date, the author has had the opportunity of observing several additional cases of this type.

The combination of an organic disease with a hysterical state superimposed is a well-known condition in ordinary practice. Common examples of this are compensation-cases in which a hysterical disability becomes attached to an injured limb, and disseminated sclerosis with hysterical symptoms of mixed motor and sensory type. In the form to be described in this chapter, the main difference is that the hysterical symptomatology is superimposed on a purely metabolic disease of the brain, in which gross organic disease of the type found in the conditions quoted as examples above is absent ; the result is a bewildering and bizarre combination of mental symptoms without apparent organic basis, which often provides a difficult diagnostic problem for the psychiatrist who is unfamiliar with the condition.

The hysteroencephalopathic syndrome is of special interest, since the fact that hysterical symptoms can be superimposed on metabolic encephalopathy in a manner analogous with that found with organic conditions is an additional suggestive argument in favour of the essentially organic nature of the encephalopathies.

(1) Characteristic Features of the Syndrome

Hysteroencephalopathy may be defined as a form of encephalopathic reaction in which hysterical symptoms are found in combination with those of metabolic encephalopathy. The principal features which distinguish the condition are as follows :—

(*i*) Mental defect and constitutional psychopathy are very commonly associated with it as compared with the uncomplicated encephalopathies. The writer has found this association in approximately 50 per cent. of all cases. The aggressive psychopathic personality, the inadequate type, the constitutional hysteric, and the dull and backward type are all found in combination with the syndrome.

(*ii*) The encephalopathic component in nearly all cases is of the dysoxic variety. In a series of fourteen cases studied by the writer, only one was definitely diagnosed as dysglycic and one was doubtful. The dysoxic component is always either of the malignant or paranoid type.

(*iii*) Hysteroencephalopathy nearly always has an acute onset, and is associated with exposure to severe stress. In a large proportion of the author's cases the breakdown had an acute onset following exposure to enemy-action.

(*iv*) The two sets of symptoms, hysterical and encephalopathic, are independent and not interconnected ; that is to say, the patient has insight into his hysterical symptoms, and these are not projected or woven into his delusions, whereas insight is defective or absent for the dysoxic symptoms.

(*v*) The prognosis is generally favourable ; of the author's original series of fourteen cases, 13 showed a good response to neurometabolic therapy, while one progressed to mental deterioration, requiring finally certification to a civilian mental hospital. The condition fulfils the dysoxic criteria in being responsive to anoxia and refractory to hypoglycæmia.

The age-incidence and mode of onset are as already described for the ordinary types of encephalopathy and neurotic depressions. There are several different modes of onset, which may be divided into those in which the early symptoms are insidious and purely those of anxiety and dysphoria, and those in which the encephalopathic symptoms reveal themselves at the commencement of the illness.

The onset may be sudden and dramatic following exposure to battle-stress, such as explosion-concussion and shock, a

succession of sleepless days and nights due to incessant action, or prolonged exposure to bombing or artillery-fire. The first symptom is not uncommonly an acute amnesic confusional episode, and may be accompanied by severe panic-reactions, syncopal attacks, or other phenomena of acute autonomic upset. In other cases there is a prodromal period of insomnia, increasing nervousness and depression, irritability, and loss of efficiency—in other words, the condition in its early stages may in no way differ clinically from an ordinary exhaustion or combat-fatigue syndrome, and this diagnosis is very often made when the patient is first seen by the psychiatrist. The frankly dysoxic symptoms often do not appear until the patient has been hospitalized for several days, when the exhaustion-symptoms fail to settle down under rest and sedation, and confusion, nocturnal restlessness, delusions, and other dysoxic features gradually make their appearance. In a third group of cases, acute confusional symptoms, in which dysoxic hallucinosis and delusions are combined with anxiety and hysterical signs, come on acutely at the commencement of the breakdown; the dysoxic features, instead of resolving, persist alongside the neurotic symptoms after the confusional features have largely cleared up.

In a large proportion of cases, exploration of the past history, work-record, and pre-encephalopathic personality reveals evidence of chronic neurotic maladjustment or dullness and backwardness.

(2) Clinical Features

The clinical picture, as would be expected, is a combination of the symptoms of dysoxia and acute neurotic depression. All the symptoms enumerated in the section dealing with the latter condition may be found, in addition to the grosser forms of hysterical symptomatology, such as paralyses, anæsthesia, tremors, and amaurosis.

The usual picture is that of a tense, fearful, and acutely depressed patient with hysterical tremor, dysarthria, acute somatic anxiety-signs such as pressure-headache and paræsthesias, hysterical fits, and panic-reactions. A variable degree of disorientation is often present, and not infrequently there is evidence of a gross amnesia of the usual hysterical type. In addition, the symptoms and signs of the dysoxic state are present, in the form of delusions, ideas of reference, and hallucinosis, which is almost always of the nociphronic form. Of the delusions,

the commonest are ideas of impending death, usually by shooting, of being about to be court-martialled and condemned, and of persecution by various agencies. Bizarre ideas of control and passivity, or of persecution by means of poison-gases, poisoned food, wireless-rays, or electricity are not uncommonly found. Delusions of self-reproach and unworthiness are very common; these usually take the form of ideas on the part of the patient that he has let down the army, betrayed his comrades, or been the direct cause of their death or other misfortunes. Hallucinations are almost always of the accusatory type, and generally take the form of voices calling the patient a coward, a homosexual, a traitor, or a Nazi.

The content of the delusional and hallucinatory material is thus largely made up of the experiences and feelings of the patient while exposed to conditions of acute combat-stress, and the mental conflicts which result from the emotional reactions to the terrifying experiences of the battlefield, such as exposure to gunfire, noise, bombing, and long periods of exposure without adequate rest and sleep.

The emotional response is the usual dysoxic one of acute depression, retardation, terror, and perplexity, coloured in addition by the concomitant anxiety and hysterical reaction. Both the simple depressed and the agitated forms of reaction are encountered.

In many cases, especially those in which there is a gross degree of confusion and agitation, the dysoxic features may be completely masked by the anxiety and hysterical symptoms. The former usually reveal themselves after a few days in hospital by recurrent nocturnal attacks of restlessness and confusion, with impulsive outbursts associated with terrifying hallucinations and ideas of reference.

The subjective symptoms of which the patient commonly complains, apart from the encephalopathic features, are of ordinary neurotic depressive type; the most usual are headache, dizziness, periods of confusion, feelings of panic and unpleasant nervous tension, shakiness, inability to concentrate, and various pains and paræsthesias of hysterical type. Their characteristic feature is that the patient has insight into them, and, unlike the hallucinations and delusions, they are not projected and ascribed by the patient to outside agency.

The above description is that of the commoner form of hysterodysoxia, in which the neurotic component is of the mixed anxiety-

hysterical type. The form associated with gross conversion-symptoms is much less common, and in this type, instead of the anxiety, depression, and apprehension described above, the affective reaction may be one of apathy and indifference approximating both to the apathy of simple dysoxia and the belle indifference of the typical hysteric. Monoplegias, anæsthesias, deafness, and amaurosis of true hysterical type may be seen in this form of hysteroencephalopathy; thus, for example, the writer has seen cases of hysterical paraplegia in combination with dysoxic depression and aural hallucinosis, hysterical deafness with depression and delusions, and hysterical paraplegia with glove-and-stocking anæsthesia associated with dullness, apathy and defective habits. These are only a few examples of the bizarre clinical combinations of symptoms which the hysteroencephalopathic syndrome may present.

The physical findings are usually completely negative, apart from somatic anxiety-signs and some degree of toxæmia in the very acute forms. In paralytic cases of long duration, trophic changes may be present in the paralysed limb or limbs.

(3) Illustrative Cases

Case 38. Motor hysteria with malignant dysoxia. An aircraftman, aged, 23, with previous negative history and six years' regular service was invalided from the Middle East theatre with a history of repeated disciplinary offences and progressive conduct-deterioration for the last two years. On admission, he was dull, confused, rambling in speech, suspicious and hostile, with a childish manner, and exhibited periods of sudden mutism and aphonia of hysterical type. He was facile in manner, and complained of typical *globus hystericus* and hearing voices which told him to attack and kill other people; while under the influence of these hallucinations he made several impulsive attacks on the ward-staff. He also showed hysterical fits and facial tics and grimaces. Physical examination was negative. The dysoxic and hysterical features responded well at first to electroanoxia but he relapsed immediately this was discontinued, and finally refused all further treatment. Hypoglycæmia produced no improvement. His condition deteriorated steadily, finally necessitating certification to a civilian mental hospital.

The striking features of this case were the combination of mixed motor and sensory hysteria with typical dysoxic hallucinosis, conduct-disorder, and confusional features. The initial favourable response to anoxia and poor response to hypoglycæmia are typical of the pure dysoxic syndrome; the ultimately unfavourable course was undoubtedly due to the long duration of the condition, the symptoms of dysoxia having been present over a period of at least two years.

Case 39. Dysoxia with motor hysteria. A private, aged 34, was admitted with a history of an acute breakdown under heavy bombing while serving in Malta. His provisional diagnosis on admission was "schizophrenia," and he was described while in hospital overseas as dull, apathetic, slovenly, and dirty in habits. On examination, he was dull, retarded, and negativistic, with mask-like expression, monotonous voice, and detached and apathetic manner. He exhibited gross hysterical tremor and palsy of the left arm, with trophic changes in the skin and nails and flexion-contracture of the hand. He also had a gross astasia-abasia with hysterical spasms of the legs. His main subjective complaints were of multiple hypochondriacal pains and dyspepsia. Memory and orientation were unaffected, and there was no evidence of delusions or hallucinosis. Physical findings were negative, apart from the trophic changes in the hand and indolent ulcers of the legs. He was a childish and feeble-minded individual of degenerate facial appearance. His encephalopathic symptoms responded well to electroanoxia, but the hysterical motor features persisted, although to some extent improved; he was finally transferred to an E.M.S. hospital for psychotherapeutic treatment.

This case is a good example of the more uncommon type of hysterodysoxia, characterized by apathy combined with gross motor hysteria. The retardation, psychomotor underactivity, and faulty habits, together with the good response to anoxia show this case to be a true example of the dysoxic state. In both the above two cases, the characteristic failure of the hysterical symptoms to improve under electroanoxia is well illustrated.

The following two cases are typical of the commoner form of hysterodysoxia, in which anxiety-signs are prominent and the hysterical features predominantly of the sensory type:—

Case 40. Dysoxia with mixed motor and amnesic hysterical features. A gunner, aged 30. He was reported as always having been "backward," with a long-standing history of hysterical tendencies in civilian life, and of concussion five years previously. He was admitted with a history of recent onset of an acutely agitated depressed state. On admission, he was acutely depressed, tense, agitated, and tearful, with mild disorientation and defective memory for recent events. He presented all the usual severe anxiety-signs, in addition to a very pronounced dysarthria which at times rendered his speech completely unintelligible, and a marked degree of histrionic exaggeration of the symptoms was apparent. Physical findings were negative. Within a few days of admission, dysoxic signs appeared in the form of persecutory delusions and aural hallucinosis. He made a good response to anoxia with abolition of the dysoxic features, but hysterical signs in the form of stammer and emotional instability persisted in mild degree up to the time of his discharge. He was a simple, childish high-grade defective, and was discharged as unfit for further military service.

Case 41. Dysoxia with sensory hysteria. A driver, aged 35, was invalided from the Italian theatre with a history of an acute depressive breakdown and delusions of self-reproach with aural hallucinosis. On admission, dysoxic features were well-marked; he was dull, confused, perplexed in manner, and was alternately vacant and retarded, and fatuous with a silly smile. He showed aural hallucinosis and expressed a delusion that everyone thought he was Hitler, and that he was about to be put to death as a criminal. Hysterical features in the form of mask-like facies, lingual tremors, tingling and numbness of the legs and cutaneous anæsthesia of the arms and hands were in evidence. Anxiety-signs were also marked, and he was at times agitated, tremulous and acutely apprehensive. The neurological examination was negative, and a definite degree of dullness and backwardness was demonstrable. His dysoxic symptoms cleared up well following anoxia, but the paræsthesias and emotional instability persisted; for this reason he was finally transferred to a neurological unit for investigation, a possible diagnosis of early disseminated sclerosis being considered. Subsequent examination, however, confirmed the original diagnosis of a hysterical condition.

These three cases illustrate well the frequent association of mental defect with the hysterodysoxic syndrome, which has already been referred to in the general clinical description.

The following case is an example of the rare combination of hysterodysglycia. The patient, a man with a long history of chronic hysterical backache, subsequently developed a typical paranoid encephalopathic state, which showed the characteristic dysglycic response to electroanoxia and hypoglycæmia :—

Case 42. Dysglycia with sensory hysteria. An aircraftman, aged 40. He had a history of many years' duration of backache without any organic basis, for which he had undergone investigation in several medical and surgical units with consistently negative findings. He also had a history of considerable recent domestic trouble, with worrying, depression, and a generally poor adjustment to service-conditions. He was reported as having recently developed persecutory delusions. On admission, he was a pale, worried-looking man, anxious and very hypochondriacal, and complained of persistent lumbar pain in addition to a variety of generalized vague aches and paræsthesias. When first interviewed, he showed no evidence of definitely dysoxic features. Physical examination revealed no abnormality apart from a slight bilateral Dupuytren's contracture of the hands. Within a week of admission, he became restless and sleepless, and complained of aural hallucinations and of persecution by poison-gas and drugs put in his food. Electroanoxia was started, but the encephalopathic symptoms showed little or no improvement ; he was therefore changed over to insulin, to which he at once showed a good response. His dysglycic symptoms cleared up completely, with partial insight, but the hysterical pains were entirely unaffected and persisted unchanged up to the time of his discharge.

The following case illustrates how, in cases of hysterodysoxia, the dysoxic features in the early stages may be completely masked by the gross anxiety-symptoms, and may only become apparent after a period of observation and careful examination :—

Case 43. A sapper, aged 40, was referred for examination with a history of recent acute depression, with aural hallucinosis, ideas of reference, and suicidal impulses. There was a long-standing previous history of nervousness, worrying, and inadequacy in civil life, in addition to two previous major breakdowns of depressive type. He had also shown a gen-

erally poor adaptation to service life. On examination, he presented the symptoms and signs of acute anxiety-hysteria, namely severe tension, generalized tremors, headache, hyperidrosis and tachycardia. He was acutely depressed and miserable, with melancholic attitude and facial expression; his memory and orientation were not affected, and there was no evidence of the hallucinosis and ideas of reference described in his medical report. Later, however, he admiited nocturnal aural hallucinations of his brother's voice speaking to him in a setting of clear consciousness; these hallucinations appeared to be of true dysoxic type. The physical examination was negative. His response to anoxia was immediate, with abolition of hallucinosis and acute depressive features, but emotional instability and anxiety-symptoms persisted in mild form up to the time of his discharge. He was a simple and childish individual of low intelligence and constitutionally inadequate personality. The final diagnosis was benign dysoxia with hysteria of sensori-motor type.

(4) Discussion and Differential Diagnosis

The differential diagnosis of the hysteroencephalopathic syndrome from organic states may sometimes present difficulties, on account of the bizarre and apparently atypical symptomatology which it presents, and the fact that its incidence includes the higher age-groups. The examination of the C.S.F., the blood Kahn-test, and if necessary the E.E.G. and radiography of the skull should always settle the diagnosis in these cases.

The following case is an example of how these cases can readily simulate an organic brain-disease :—

CASE 44. An R.A.F. corporal, aged 31. He was admitted with a history of having been found wandering in a state of acute amnesic confusion. His relatives stated that for several weeks he had been very depressed, ill in appearance, and peculiar in behaviour, and his wife gave the information that he had always been liable to sudden outbursts of temper and very difficult to get on with when at home. On admission, he was correctly orientated with remote memory not greatly affected, but a definite circumscribed massive amnesia was present. His facial expression was mask-like, and his manner childish and fatuously euphoric, with garrulous and inconsequent flow of talk and complete lack of insight. He showed tremors and a moderate dysarthria, and the clinical picture was strongly suggestive of early general paresis. Pupillary

and other C.N.S. abnormalities were, however, absent, and the C.S.F. and blood-serology normal. Within a few days of hospitalization, dysoxic symptoms appeared in the form of agitation and depression, with periods of acute confusion and delusions of unworthiness and self-reproach. These responded well to electroanoxia, but the childish manner, emotional lability, and lack of insight were unchanged. The patient was finally discharged to the care of his relatives, mentally much improved.

Epileptic conditions may present difficulties, especially those of the type in which convulsive phenomena are absent and the symptoms of predominantly psychic form. This is especially so, since such features as episodes of mental confusion, impulsive outbursts, ideas of reference, and aural hallucinosis are commonly found in masked epilepsy of the psychical type, which may imitate the hysterodysoxic syndrome extremely closely.

The principal diagnostic points are the absence in epilepsy of the gross anxiety and hysterical phenomena seen in hysteroencephalopathy, and the electroencephalogram, which should always be done in cases where there is any element of doubt. The diagnosis of an epileptic state should never be made in the presence of a normal E.E.G., even when minor convulsive phenomena are present, since pseudo-epileptic syncopal attacks of epileptiform type occur sometimes in encephalopathy, and are in all probability due to the metabolic disturbance, and not to congenital dysrhythmia cerebralis.

The acute neurotic depressions and psychopathic states often bear a strong clinical resemblance to hysterodysoxia, especially when there is present a marked degree of disorientation, dysphoria, and conduct-abnormality. The differential diagnosis depends on the fact that in these conditions dissociation and projection as shown by the presence of true hallucinosis and delusions are absent; the presence of these symptoms in combination with those of hysteria is the only criterion for the diagnosis of hysteroencephalopathy.

In acute neurotic and hysterical states, the terrifying battle-dreams, nightmare-states, and hypnagogic phenomena have to be carefully distinguished from true dysoxic hallucinosis. One of the commonest diagnostic mistakes made in dealing with cases of this type is that of confusing hypnagogic phantasies and dream-states with true hallucinations, with the result that these patients

are not uncommonly labelled as encephalopathic and subjected unnecessarily to neurometabolic therapy. The presence of hallucinations in a setting of clear consciousness is, of course, diagnostic of dysoxia ; but it must be borne on mind that both types of sensory experience may occur in a confusional setting both in the hysterodysoxic and the pure neurotic depression.

True encephalopathic delusions have to be distinguished from the obsessive ideas of victimization and morbid self-consciousness already described as occurring in the psychopathic and some hysterical states. In these conditions the bizarre autochthonous ideas and feelings of passivity of the dysoxic do not occur, and the ideas of persecution always have a strong factual basis.

The ordinary depressive variety of hysterodysoxia may easily be mistaken on superficial examination for the malignant dysoxic state. The differential diagnosis is important, for the former disorder, as already pointed out, has on the whole a very good prognosis. The points to look for in true malignant dysoxia are the profound degree of apathy and perplexity with orientation comparatively unimpaired, faulty habits, repeated attacks of confusion, dyssymbole, and absence of anxiety and hysterical features. The presence or otherwise of hallucinations and delusions is not a reliable guide, as the same type occurs often in both conditions.

In malignant dysoxia, there is always a peculiar and bizarre quality in the symptoms, which is very characteristic and often extremely difficult to describe adequately in words. It can only be appreciated by actually seeing and examining a large number of these cases, and to the trained observer is often the most striking of all the symptoms and can be detected at a glance.

Dysglycic states offer little or no difficulty, on account of their characteristically bizarre and peculiar symptomatology. The question of their diagnosis when secondary anxiety-symptoms are present has already been discussed in the chapter on dysglycic brain-disease.

The derealization type of dysoxia is, as a rule, readily distinguishable by its characteristic triad of symptoms, and by the extreme rarity of gross anxiety and hysterical features in its symptomatology.

(5) Prognosis

The prognosis is, as a rule, very favourable. The exception is those cases in which the dysoxic component is of the malignant

instead of the more usual paranoid-depressive type, as in Case 38 of the series described. Generally speaking, the prognosis is the same as for uncomplicated dysoxia, and the presence of the hysterical symptoms does not appear to have an adverse effect on the outlook for the dysoxic component. Neither does the presence of mental defect or psychopathy, in the same way as in the ordinary forms of uncomplicated dysoxia.

The dysoxic symptoms respond readily to electroanoxia, but the hysterical features are much more resistant as would be expected, and tend to persist for a varying period after the dysoxic symptoms have resolved. In the hysterodysglycic form, the prognosis is in general the same as for the ordinary pure dysglycic states.

(6) Treatment

Treatment resolves itself into that of the encephalopathy, which is naturally the most important, and that of the hysterical symptoms.

Treatment of the encephalopathy is by the usual method of electroanoxia or hypoglycæmia, according to the type of metabolic disorder present. This is dealt with in detail in the ensuing chapter, and in essentially the same as that laid down for the ordinary dysoxic and dysglycic states. In the dysoxic forms, the usual number of convulsions required in order to effect remission is seven to ten, the optimum frequency of application being thrice weekly.

The anxiety and hysterical symptoms generally tend to improve *pari passu* with the dysoxic features, although neurotic residua in the form of timidity, lack of confidence, mild anxiety and emotional instability of varying degree may persist for a considerable period after the dysoxia has resolved. They usually tend to clear up gradually with or without adjuvant treatment. Their treatment consists of occupational therapy and simple psychotherapy, combined with appropriate medication. No drug-treatment appears to be specific; in cases where anxiety and tension are the principal residua, a bromide mixture or luminal in doses of gr. $\frac{1}{2}$ three times daily is often beneficial, while in patients whose complaint is chiefly of mild depression and asthenia, benzedrine in dosage of 10 to 15 mgms., twice daily, is sometimes of help. Persistent insomnia and nightmares

should always be treated by hypnotics in full dosage, such as medinal gr. 10 or sodium amytal gr. 6 on retiring.

It is important to bear in mind that, once the dysoxic features have resolved, it is useless to persist with electroanoxia in the hope of further influencing the neurotic residua. Such a course may, indeed, actually do more harm than good, on account of the fear and apprehension which the treatment may induce in some patients, particularly those of the tense and over-anxious type. This last point emphasizes the inaffectiveness of neurometabolic therapy generally in the treatment of purely psychoneurotic conditions which are not due to metabolic brain-disease; and the author is in agreement with the majority of psychiatrists that in such conditions the applications of neurometabolic therapy are extremely limited, psychotherapeutic procedures being in nearly all cases the method of choice.

CHAPTER XII

THERAPY OF THE METABOLIC ENCEPHALOPATHIES

(1) Introductory

No branch of medicine has within recent years been so productive of ill-timed optimism, acrimonious argument, sensational publicity, and hostile criticism as have the anoxic and hypoglycæmic forms of therapy for mental disorders. At its inception, this form of treatment was enthusiastically hailed by its protagonists as the possible panacea for all the major forms of mental disease; later, however, when more sober observation and critical analysis had demonstrated its pitfalls and fallacies, psychiatric opinion swung somewhat violently towards the other extreme; indeed, one eminent neurologist, with more emotion than clinical acumen, went so far as to declare that no clinician with any respect for the human cerebrum would ever condone the administration of convulsive therapy to this delicate organ.

In order that a balanced and reasonable attitude of mind towards the problem may be acquired, before actually discussing the technique and results of neurometabolic therapy some general points and analogies with the methods employed in general medicine will first be discussed, and the pitfalls and limitations attendant on these forms of therapy briefly considered.

(2) Objections and Arguments against Neurometabolic Therapy

The principal objections brought forward by writers of the more conservative school of psychiatric opinion are the following; first, that procedures such as the induction of therapeutic convulsions and insulin-coma are a barbarous and crude form of treatment; second, that they are by no means always a therapeutic success, and that encephalopathic patients often recover in any case without the aid of specific therapy; thirdly, that such therapy does not prevent subsequent relapses; fourthly, that it only removes the symptoms without dealing effectively with the underlying psychological conflicts and difficulties; and fifthly and lastly, that it may inflict permanent organic damage on the brain-tissues, in addition to producing a host of other catastrophic complications, including fractures and dislocations, myocardial

damage, pulmonary infections, and general physical deterioration. These objections will now be examined and considered in detail.

The first objection is easily dealt with; the therapeutic induction of convulsions is no more crude or barbaric a procedure than the induction of malaria for the treatment of general paresis, or the resection of several feet of bowel for carcinoma of the colon, or indeed, than several other even more massive and daring adventures in everyday general surgery.

The second argument is one which can be applied to almost any other of the several potent remedial agents known to general medicine; there is no known agent which is a specific one hundred per cent. panacea for any group of morbid conditions. Spontaneous recovery is known to occur in a number of grave conditions in medicine, examples of which are lobar pneumonia and cerebrospinal meningitis; nevertheless, no modern clinician would hesitate to use such potent remedies as the sulphonamides and penicillin when confronted with these diseases. Similarly, the fact that spontaneous recovery does occur in some forms of encephalopathy is not a valid argument against the use of the anoxic and hypoglycæmic therapies. Moreover, nearly all psychiatrists agree that the timely exhibition of electroanoxia in a severe dysoxic depression can cut short the patient's suffering and effect dramatic symptomatic relief from mental agony which might otherwise be prolonged for many months or even years (in the involutional forms), before a spontaneous recovery finally occurs.

The same argument is valid for the third objection, namely that neurometabolic therapy does not prevent relapse. This is certainly true to a large extent; but in the same way, a future attack of pneumonia or meningitis cannot be guaranteed against by the use of sulphonamide or penicillin therapy. Yet in spite of this, no modern clinician will dispute the value of chemotherapy in these conditions. As far as the writer's knowledge goes, not even the most enthusiastic advocates of the neurometabolic therapies have ever made the claim that they confer complete and permanent immunity against future attacks of dysoxia or dysglycia.

The fourth objection is partially valid, insofar as neurometabolic therapy is not the whole answer to the psychological stresses and difficulties which are known to predispose to these disorders, and which can in most cases only be dealt with by means of adequate after-care and ancillary psychotherapy. The

point is, however, that when the patient is brought for treatment, the problem to be dealt with is essentially an organic cerebral condition, and until this has been treated by the appropriate biochemical measures, any kind of psychotherapeutic or other general measures are foredoomed to failure. It would be about as sensible to suggest that cerebral tumour or general paresis could be treated effectively by psychotherapeutic methods without recourse to surgery or malarial therapy. This is, of course, not an argument intended to decry the uses and possibilities of purely psychotherapeutic forms of treatment, the place and importance of which will be fully discussed in the appropriate section of this chapter.

The fifth objection, that neurometabolic therapy may produce organic cerebral damage and intellectual deterioration, can be easily disposed of. In the whole series of cases treated by the author during a period of more than five years, no case was encountered showing permanent residua in which the mental enfeeblement could not have been attributed to the encephalopathic process; the opponents of neurometabolic therapy have never as yet ventured to explain why the residual brain-damage in such cases should not be the result of the morbid process rather than that of anoxic or hypoglycæmic therapies. It would seem to the writer to be as reasonable to suggest that, in cases of paresis which have remitted with residual dementia following malarial treatment, the permanent mental changes are the result of the malarial and not of the spirochætal infection. Moreover, neuropathologists are by no means in agreement that organic damage to the brain does result in the human subject as the result of therapeutic convulsions and hypoglycæmic coma. With regard to the other complications, such as fractures, dislocations, and cardiac disturbances, the same argument could be applied equally well to any of the other therapeutic procedures of general medicine and surgery, none of which are entirely free from risks and complications. Statistics have shown that the actual mortality of anoxic and hypoglycæmic treatment in the hands of experienced workers is extremely small, while the risks are certainly no greater than those of surgical anæsthesia in the hands of an experienced anæsthetist. In the writer's series of cases, the major complications described in the literature have been extremely rarely encountered.

(3) The Limitations of Neurometabolic Therapy

The criticisms which have been most frequently levelled against the use in psychiatry of these forms of treatment have now been dealt with, and their limitations will now be briefly discussed.

It should be made clear firstly that neurometabolic therapy cannot resuscitate and restore to normal function neurones and association-tracts which have been destroyed or irreversibly damaged as the result of metabolic changes of long duration—in other words, it is clinically ineffective or only partially effective in chronic cases. For all practical purposes a chronic case may be regarded as any one which has more than six months' duration of symptoms; this is certainly true as far as the malignant dysoxias and dysglycias are concerned. The importance of early diagnosis and prompt institution of energetic therapy has already been stressed in this connection.

The second point to be emphasized is that neurometabolic therapy will not cure mental deficiency or constitutional psychopathy. When the writer was first employed in civilian life as a junior medical officer in a civil mental hospital, he was placed in charge of the insulin-therapy unit, but was not able to select his own cases for treatment. It was surprising how many cases of feeblemindedness and psychopathic personality were referred for treatment by the senior medical officers, presumably in the fond hope that a course of hypoglycæmia would enable a mental defective to grow a new and more complex cortical cytoarchitecture. In the same way, the constitutionally inadequate schizoid and the chronic worrying obsessional personality cannot be transformed into average normal individuals by means of such therapeutic procedures. The old proverb about the silk purse and the sow's ear certainly holds good in the case of the neurometabolic therapies. It should, however, be indicated in this connection that the treatment is as effective for the cure of encephalopathy occurring in the mental defective and psychopath as for that in patients of previously normal intellectual capacity.

The third limitation—the impossibility of guaranteeing any given case against subsequent relapse—has already been discussed. Suffice it to say that, in the vast majority of cases which treated adequately in the early stages, the probability of relapse is, in the writer's experience, no greater than in those cases which exhibit spontaneous remission.

Finally, anoxic and hypoglycæmic therapy are emphatically not a universal panacea for all forms of mental disorder, any more than, say, penicillin or the sulphonamides are a universal answer to all forms of bacterial and viral infection. Apart from a few cases of obsessional neurosis and anxiety with dysphoria, its efficacy and range of application are confined entirely to the metabolic group of brain-disorders. It is of no value in the treatment of demonstrably organic reaction-types, such as general paresis, arteriosclerotic, and senile encephalopathies, unless there is evidence of a coexisting metabolic derangement, as has already been indicated in the section on the post-traumatic forms of dysoxia and dysglycia.

(4) Its Potentialities

Neurometabolic therapy is specific for the metabolic encephalopathies in the same way as arsenical drugs are for syphilis, or penicillin for certain types of bacterial infection. This statement requires two qualifications ; first, the case must be in the early stages of the disorder, before irreversible neuronic changes have set in, and secondly, the correct form of therapy must be given, according to whether the case is dysoxic or dysglycic in type. It is just as futile to treat an excited dysglycic by anoxia as it is to submit a stuporose dysoxic to prolonged hypoglycæmic therapy. Provided these qualifications are fulfilled, a favourable outcome may be expected in approximately 75 per cent. or more of early cases so treated.

It has a direct action upon the metabolic process, in contrast to the earlier forms of treatment such as prolonged narcosis, the effect of which is simply the superimposition of a state of narcotic poisoning on the already unhealthy cerebral cells, without affecting the essential underlying metabolic disturbance. It can abort the encephalopathy in the early stages, and effectively prevent deterioration and subsequent dementia. In addition to its specific metabolic action, it exerts a dramatic effect on symptoms, both mental and physical, such as toxæmia, restlessness, refusal of food, and degraded habits. Thus, in cachectic and toxic dysglycics, the acute restlessness and toxæmia disappear rapidly and dramatically within a few days of commencing hypoglycæmia, while in depressed dysoxics early and energetic use of electroanoxia is the surest safeguard against the possibility of a sudden impulsive suicidal attempt. Recent work with war-

time psychiatric cases has also shown that insulin therapy in modified form has a definite value as a symptomatic treatment in certain types of acute anxiety and exhaustion syndromes; while electroanoxia does appear to benefit some types of obsessive-ruminative and anxiety-states in which dysphoria is a prominent symptom, although, as already pointed out, its field of application in the psychoneuroses as a whole is much more limited.

It has also a very definite value as a purely diagnostic procedure, both for differentiating the dysoxic and dysglycic forms of acute confusional reaction, and in the diagnosis of dysoxic dysphoria from the acute personality-disorders and neurotic depressions. Reference has already been made to this in the chapter dealing with the last-mentioned conditions and their differential diagnosis.

(5) Indications and Selection of Cases

The treatment of the metabolic brain-disorders may be conveniently divided into general physical and medical measures, specific biochemical procedures, psychotherapy, and the treatment of residual symptoms. For purposes of the present discussion, the second of these only will be considered, the other three being dealt with separately in a subsequent section of this chapter. Before describing in detail the technique and management of the anoxic and hypoglycæmic treatments, some general observations on the indications and selection of cases for neurometabolic therapy will first be presented.

The indications for specific therapy may be conveniently considered under the headings of why to give neurometabolic therapy, when to give it, how to give it, and last but certainly not the least important, when not to give it. Special emphasis should here be laid upon the last point, since it has been found that in certain types of case unpleasant and even highly disastrous results may ensue as the result of over-enthusiasm in the use of these treatments, to which the writer must plead guilty to having subscribed on one or two occasions during the earlier part of his experience with the neurometabolic therapies.

(i) *Why to give Neurometabolic Therapy.*

The object of the physician who attempts any major form of specific treatment is firstly to relieve the patient's symptoms, and secondly, to attack directly, if possible, the underlying morbid

process. The object of neurometabolic treatment is to counteract and arrest the encephalopathic process ; to relieve the distressing mental symptoms, such as depression, unpleasant hallucinations, and bizarre paræsthesias ; to rapidly suppress objectionable features, such as restlessness, destructiveness, refusal of food, and toxæmia ; to obviate the repeated use of powerful narcotics and hypnotics ; to cut short the course of the disease and so shorten the duration of the patient's incapacity and stay in hospital, and restore him to a useful social and working level as soon as possible ; to induce rapid and permanent amnesia for his terrifying encephalopathic experiences ; and finally, to render the patient accessible to psychotherapy and other ancillary therapeutic measures.

(ii) *When to give it.*

It may generally be stated that the optimum time for instituting biochemical therapy is as soon as the diagnosis of metabolic encephalopathy has been definitely confirmed, in other words, at the earliest possible moment. The importance of first excluding organic causes has already been discussed in the chapter on differential diagnosis of the encephalopathies.

In acute cases, the absolute indications for immediate specific therapy are severe toxæmia and wasting, continual restlessness, persistent refusal of food, and evidence of progressive deterioration of the patient's mental and physical condition, especially if there is no improvement after a few days of tube-feeding, sedation, intensive nursing, and other general measures. This is especially important in the acute confusional types of dysoxia and dysglycia, which often deteriorate and become cachetic and dehydrated with alarming rapidity. These cases are often among the most desperate type of medical emergency, and here early and energetic specific therapy may be a life-saving measure. It is most important to emphasize that treatment should be begun before the patient reaches a severe degree of cachexia and emaciation, and in the writer's view expectant treatment in these cases is only justified when the symptoms begin to show evidence of spontaneous amelioration within a day or so of admission to hospital.

An important consideration to bear in mind in connection with these fulminating cases is the possibility that irreversible changes may be produced in the brain-tissues within the first few days or weeks of the disorder, so that delay in instituting treatment may result in permanent damage and mental crippling,

even though the florid encephalopathic symptoms may finally resolve completely.

In benign dysoxia of the simple depressive type, the problem is entirely different, since these cases have little or no tendency to dement, and spontaneous recovery is the rule, especially in those with a previous history of depressive attacks with spontaneous remission. In these cases therefore the use of conservative treatment may often be justified. The indications for commencing anoxic therapy in this type of illness are acute mental suffering and distress demanding prompt alleviation, marked suicidal tendencies, persistent refusal of food with progressive loss of weight, and the appearance of bizarre features suggestive of malignant dysoxia. It should be remembered that an acute encephalopathic depression occurring for the first time in a patient under the age of thirty years is almost certainly of the malignant dysoxic type, unless there is a clear history of one of more previous such attacks with spontaneous remission. The diagnosis of benign dysoxia should always be gravely suspect when occurring for the first time in this age-group, particularly if there is evidence of disorientation, perplexity, and dyssymbole in the form of bizarre sensations and inability of the patient to describe his symptoms.

In milder cases where the above urgent considerations do not operate, the general rule is that treatment should be instituted as soon as there is no evidence of response to conservative measures, or if symptoms suggestive of malignant dysoxia or dysglycia supervene. Some paranoid forms of both types show a tendency to spontaneous remission when once the patient has been removed from this previous environment to a hospital, and the precipitating stresses which originally determined his breakdown have ceased to operate.

Generally speaking, the possibility of spontaneous remission should never be relied upon, except in the occasional specific instances described above. The common assertion that a large proportion of acute encephalopathies of wartime tend to spontaneous recovery has not been confirmed by the writer's experience, and the course and prognosis in nearly all such cases has been found to differ in no respect from that of the ordinary civilian type of case encountered in mental hospital and out-patient practice.

(iii) *How to give it ; the technique of Electroanoxia.*

The biochemistry and physiological changes produced by electroanoxia are described in detail in the ensuing chapter. The actual technique advocated and practised by the writer differs in no essentials from that laid down in the standard text-books on the subject, except as regards one or two minor details.

For the acute malignant dysoxias, electroanoxia is administered once daily for the first five applications, or until definite evidence of improvement is manifested. The writer has found that in the most acute forms administration thrice weekly or on alternate days is usually ineffective, a cumulative effect being apparently essential. Application on alternate days results in transient mental improvement, the patient relapsing into his confused and bewildered state within a few hours of each application. Often little or no improvement is apparent for the first three or four applications, but after five or six convulsions have been given, a sudden and dramatic improvement is evident. At this stage, the mutism, restlessness, and mental confusion show a striking diminution, and the patient is then changed over to the second stage of therapy, in which it is given on alternate days only. Remission with insight is usually obtained after eight to ten convulsions, that is, about fourteen days on the average after commencing treatment. As previously stated, however, relapse within a week or so after discontinuation is the rule rather than the exception in these cases, and should be treated on the same lines as described above. It is usually found that fewer convulsions are required to effect remission than for the primary attack, five to six being the usual number. If a second relapse occurs, treatment as outlined above should be repeated, and a series of three courses totalling altogether perhaps 18 to 20 applications may be necessary to effect a lasting and stable remission. In spite of this relapsing tendency, the ultimate prognosis is generally good, if the case is an early one ; in a few such patients, however, repeated attacks of mental confusion occur in spite of all treatment, which progress steadily and remorselessly to deterioration and dementia. The writer has tried various agents in these cases for the prevention of relapses, including benzedrine and thyroid in large doses, and sedation, none of which appear to be of any value. The only reliable prophylactic in such cases at present appears to be maintenance-doses of electroanoxia of one to two convulsions weekly, until the patient shows evidence of becoming finally stabilized.

Acute paranoid dysoxia is treated on the same lines as for the malignant form, acutely suicidal tendencies and distressing hallucinosis being regarded as the absolute indications for energetic therapy. The total number of applications required to effect remission is usually nine to ten, and this form generally shows much less tendency to relapse than the malignant type.

The indications for electroanoxia in the benign form are the same as for the paranoid type. The response is immediate and dramatic, two to four applications usually being sufficient to effect remission, and the tendency to relapse is much less marked than in the malignant form. In very acute cases, application daily for the first three to four convulsions may be advisable.

The less common manic form is rather more obstinate, and requires approximately eight to ten applications in order to effect remission. Treatment is given in these cases daily or thrice weekly, according to the severity or otherwise of the symptoms.

The treatment of the hysterodysoxic and derealization-forms differs in no respect from that described for the typical dysoxias. In the case of the last-named condition, a course of five to six applications is usually sufficient to obtain remission.

To sum up, it may be stated that acute depressions, stupors, katatonic and confusional states are the forms of dysoxia which the most susceptible to electroanoxia, and which show the most striking therapeutic response. Next in order of susceptibility come the paranoid and derealization-types, the manic form being least susceptible of all.

As regards the actual technique of application, two important points should be noted here. The first is the importance of shaving the hair over the temporal regions and keeping it short throughout the period of active treatment, and of thoroughly cleaning the temporal skin area with ether-soap and spirit prior to the application of the electrodes. The combination of human hair and human grease is one of the best electrical insulators, and subconvulsive doses with repeated application of the current should be avoided as far as possible. Subconvulsive doses are entirely useless therapeutically, and their only effect is to raise the head-resistance and convulsive threshold, in addition to greatly increasing the tendency to post-anoxic headache and mental confusion. It appears likely that they also increase the tendency to acute cardiovascular syncope, which alarming complication

will be further referred to in a later section of this chapter. A form of headband giving as tight a contact as possible should always be employed.

The second point is that it appears from the author's observation that the therapeutic effect of the convulsion varies directly as the degree of cyanosis obtained during the convulsive phase. This is what would be expected from theoretical considerations since cerebral anoxia is now generally considered to be the most important single physiological mechanism concerned in the process of improvement. The degree of cyanosis produced is a measure of the intensity of the cerebral anoxaemia, and the writer has found generally that those patients who display a marked degree of cyanosis and parasympathetic activity seem to do better than those in whom these effects are not so well marked. A slight increase in the voltage and timing—usually O.I. second and 5-10 volts is usually effective in producing the desired degree of cerebral anoxia.

Technique of Hypoglycæmia.

The indications for the institution of hypoglycæmic therapy have already been outlined. As in electroanoxia, the technique employed by the writer does not differ in its essentials from that followed by other workers at the present day, except for the following points; resuscitation is carried out by means of the intravenous method in all cases, the dosage of intravenous glucose administered being 40 ccs. of 33 per cent. glucose solution, and the patient being given a high-carbohydrate meal of bread and butter with jam and sugared tea immediately on awakening This method dispenses with the large feed of oral glucose, and has been found to give perfectly satisfactory results. The incidence of after-shock is found to be no greater than with the orthodox method, and the advantage is that a great economy in the amount of glucose used is effected, an important consideration under conditions of strict rationing such as obtain to-day. In cases with very poor veins, the oral method of giving 14-16 oz. glucose by tube-feed is used to awaken the patient from coma.

The initial dose of insulin on commencing treatment is 30 units the first day, increased by 10 units each day until coma-level is reached. This comparatively large dosage and proportionate increase ensures that the patient is rapidly brought under the influence of the insulin, an important consideration in very severe cases, and has been found to be perfectly safe. In very cachetic

and toxic patients, a much smaller initial dose is used, of the order of 10-15 units, and increased by 5 units or less until coma-level is attained.

No special investigations are made prior to commencing treatment, apart from a routine physical examination to exclude the presence of organic disease. Preliminary blood-sugar tolerance tests are in the author's experience of little value as a guide to the patient's susceptibility or otherwise to insulin, and would appear to be almost entirely of purely academic interest.

In the acute malignant dysglycias, the response to hypoglycæmia is prompt and dramatic, physical improvement being as a rule apparent after the first half-dozen injections and long before the actual coma-dose is reached. Of the mental symptoms, the restlessness and degraded habits are the first to show amelioration, after which the hallucinations, delusions, thought-disorder, affective abnormality, and lack of insight improve in the above order.

The usual number of comas required to attain remission in early dysglycia is of the order of 15 to 20, a much smaller number than is usually found in the more chronic type of case met with in civilian practice. Failure to show improvement when this number of comas has been obtained usually indicates a poor prognosis. The two other bad prognostic signs are failure to reach coma when a dosage of the order of 150 units has been attained, and progressively increasing insulin-resistance—that is to say, when once coma-dosage has been reached, the patient tends to gradually require progressively larger doses in order to maintain the coma-threshold. Conversely, insulin-sensitivity—that is to say, when the patient tends to go into coma on progressively smaller doses each day—nearly always indicates a favourable prognosis.

The paranoid type of dysglycia, which is usually of longer duration than the ordinary malignant form, requires usually a longer course and greater number of comas to ensure remission, thirty to forty being the average number. Improvement, as would naturally be expected, is neither so rapid or so dramatic as with the malignant form.

The mixed or combined dysglycic-dysoxic syndrome always requires hypoglycæmic therapy. As pointed out previously, these cases, if treated by electroanoxia while in the dysoxic phase of their encephalopathy, show temporary improvement only to have a dysglycic relapse at a later date, characterized by hallucinosis,

delusions, and other typically dysglycic features. More rarely, a case of this type may be precipitated from dysoxic depression straight into a state of dysglycic excitement as the result of anoxic therapy. Their treatment and prognosis is the same as for the pure dysglycic type. In cases of this type which fail to make progress under hypoglycæmia, the combined method of anoxic-hypoglycæmic therapy is sometimes useful; the writer's practice has usually been to give ordinary hypoglycæmia three days a week, alternating with hypoglycæmia plus electro-convulsion on the other three. The optimum time for administration of the anoxic convulsion is during the third hour after injection, when the patient is passing into coma and in the irritable myoclonic state. Termination of the coma is always carried out by tube-feeding immediately after cessation of the convulsion, a rest-day usually being given on the day following if the after-effects of the convulsion, such as headache and confusion, have been unduly severe.

As regards the optimum duration of coma, the writer has found that in cases of pure dysglycia an average duration of one to one and a half hours in coma each day to be effective, longer than two hours being generally regarded as carrying a considerably greater risk.

The method of administration of the insulin is important. The writer has found that the intravenous route does not seem to offer any advantage over the intramuscular, particularly in patients with poorly marked veins. In using the intramuscular route, it is essential to use a long needle of fairly wide bore, giving the injection deeply in order to ensure that it goes into the muscle and not into the subcutaneous fat; failure to ensure this usually results in failure of the patient to pass into coma with prolonged restlessness and struggling.

(iv) *When not to give it; contraindications.*

The contraindications for neurometabolic therapy may be divided into physical and mental, of which the former will be dealt with first.

Of the two forms of therapy, electroanoxia carries the greatest risk of cardiovascular syncope and reactivation of latent physical disease, by reason of the sudden intense stress which it imposes on the heart and vascular system. For this reason uncompensated heart-disease, active pulmonary tuberculosis, and a severe degree of cachexia are the absolute contraindications against this

form of treatment. Insulin therapy, on the other hand, can usually be given without danger in the presence of the above conditions. Pulmonary tuberculosis is unlikely to be reactivated by hypoglycæmia, whereas electroanoxia seems to carry a very definite risk of flare-up in quiescent cases (*vide* Case 7, Chapter V). Patients with well-compensated valvular heart-lesions, whether mitral or aortic, stand both forms of treatment well, although older patients with fatty or degenerative myocarditis are bad subjects, showing a marked tendency to sudden heart failure under hypoglycæmia.

In very cachectic dysoxics, who are too feeble to stand anoxia, a short course of modified insulin may first be given to promote appetite and improve the general condition prior to commencing electroanoxia.

Of other physical conditions, pregnancy and advanced age are not necessarily contraindications, provided the patient is free of organic disease. Electroanoxia has been used with success in pregnant women, and involutional patients up to the age of sixty are often among the most striking successes of this form of treatment. The other physical conditions which contraindicate neurometabolic therapy are those laid down in the standard text-books, and for practical purposes may be considered to be the same as those for general anæsthesia.

As regards electroanoxia, the contraindications to this which do not apply to hypoglycæmia are recent fracture or *fragilitas ossium*, severe cachexia, and evidence of constitutional autonomic instability with tendency to syncope. This last-named contraindication will be further discussed in connection with the complication of acute cardiovascular collapse following the convulsion. The question of cardiac disorders of organic type has already been discussed under the subject of general contraindications.

With regard to purely mental contraindications, it may be generally stated that electroanoxia is contraindicated in cases of dysglycic excitement, whether of the malignant or simple manic type. It not only fails to effect any improvement, but often tends to make the excitement and impulsive tendencies worse, and hypoglycæmia is always the correct form of treatment for these conditions. The same remarks apply to a lesser degree in the more chronic paranoid type of dysglycia.

Hypoglycæmia should not be used for depressed dysoxics with apathy and confusional symptoms, except as a preliminary measure as described for very ill and cachectic cases of this type.

In the former type of case, it often makes the confusion and retardation definitely worse. Similarly, it is ineffective for the paranoid form of dysoxia, in which it seems merely to exacerbate the delusions and hallucinations.

There is one type of patient of particular interest, in which all forms of neurometabolic therapy appear to be definitely contraindicated. This is the very chronic encephalopathic of many years duration, whose symptoms are very mild, and who shows little or no deterioration and has managed to make a more or less satisfactory adaptation to reality and carry on a reasonably normal existence. In such cases, the residual symptoms are due to irreversible cerebral changes, and often the only effect of, neurometabolic therapy is, so far from producing improvement, to cause a sudden flare-up of symptoms, usually in the form of an acute hallucinatory-confusional episode. In the first flush of enthusiasm for the new methods of treatment, the writer treated several of these cases with hypoglycæmia and anoxia, all with unfortunate results. The following two cases from a series of military patients are a good example of the unfortunate sequelæ which may sometimes result from the injudicious use of neurometabolic therapy :—

Case 45. A corporal, aged 35, was invalided from the Middle East with a history of dysglycia of paranoid type. Fourteen years previously he had had a similar attack, in which he imagined that people talked about him and said that he had "body-odour." This episode apparently resolved partially, and he was able to adapt and carry on a normal life, his only residual symptom being a persistent bizarre sensation in his head localized to the left parietal region. He was passed A1 for the army and adapted fairly well to service-conditions, but had an acute exacerbation of his dysglycic symptoms soon after drafting to the Middle East, and developed delusions that everyone talked about him and said he was a homosexual; these delusions and ideas of reference were still in evidence when he was admitted. He was started on insulin, reaching a dosage of 150 units without coma. The result of the treatment was that his paræsthesias and ideas of reference became considerably worse, necessitating abandonment of the treatment.

Case 46. A gunner, aged 32, was invalided from the Middle East with a history of paranoid dysglycia. His original breakdown had occurred 11 years previously, with

one acute exacerbation three years later. Although a man of superior education and upbringing with a university career and first-class degree in languages, he had never been able to hold a job, and had drifted aimlessly throughout his life. He had been treated for his original breakdown by psychoanalysis, and had never been admitted to a mental hospital. On admission, he was sullen, suspicious, hostile, and overbearing in manner, with numerous paranoid ideas of reference and a fixed delusion that he was being hypnotized by some unknown persons for his own good. Later he became more co-operative and tractable, but remained solitary and apathetic with delusions and paranoid ideas as described above. At his own request, anoxia was started ; after three treatments he became tense, anxious, and much more unstable, stated that he felt much worse, and begged that the treatment should be stopped. He was discharged home unimproved.

These two cases are good examples of how a mild chronic encephalopathy can be exacerbated as the result of injudiciously-applied neurometabolic therapy. The actual explanation of this phenomenon is obscure ; it appears probable that in these cases the damaged cerebrum is able after a time to maintain a partially normal but precariously balanced metabolic equilibrium during the quiescent stage of the disorder, which is completely thrown out of gear by the sudden metabolic changes produced as the result of the treatment. Fortunately, the acute exacerbation so produced is always temporary, and quickly clears up spontaneously on cessation of the treatment. In both these cases, the salient points were the long duration of the disease, its mild character, the age of the patients, and the fact that in both cases the encephalopathy was of the paranoid dysglycic type.

It is the writer's view that in this type of case any form of biochemical therapy is absolutely contraindicated, and that the correct form of treatment for these patients consists of psychotherapeutic measures, occupational therapy, and congenial employment. This is the only form of metabolic encephalopathy in which psychotherapeutic methods alone are of real value.

Finally, hypoglycæmia seems to be definitely contraindicated in cases of the derealization and obsessive-ruminative syndromes, in which there is much degree of depression and unpleasant tension. As with the ordinary forms of dysoxia, these patients appear in many cases to be made worse as the result of this

treatment. Electroanoxia is always the treatment of choice in these cases.

(6) Complications

No major complications have occurred in any of the writer's series of cases treated by hypoglycæmia. The most frequent minor complications were delayed recovery, after-shock, and headache with mental confusion following a hypoglycæmic convulsion, all of which responded to the usual measures.

The major complications commonly reported in the literature as accompanying electroanoxia have been very rarely encountered. As regards fractures, the writer has seen not more than half-a-dozen in the whole of his experience, both military and civil ; of these, one was scapular and the rest vertebral. In the case of scapular fracture, this was the result of a subconvulsive dose, the fracture being apparently produced solely by the violent jerk which occurs at the moment of passing the current ; this would appear to indicate that the initial momentary clonus may be the cause of some of these fractures, rather than the actual tonic-clonic stages of the convulsion, as is generally believed. In conclusion, it is the author's opinion that the risk of fractures in the course of electroanoxic therapy is one which has been grossly exaggerated, and that the use of paralysant drugs to control the muscular contractions is quite unnecessary. In the author's series of cases, no special precautions were taken to guard against fractures, apart from maintaining the patient in a position of extension during the application of the current.

The most alarming major emergency in electroanoxia—fortunately quite uncommon—is acute cardiovascular syncope. It occurs most commonly in cases where more than one application of the current has to be made in order to produce a convulsion. The clinical symptoms and mechanism appear to be similar to those of the " primary cardiac failure " of chloroform anæsthesia, and are probably due to over-stimulation of the vagus centres by the current, with inhibition of the heart-beat and respiration. After the termination of the clonic stage and period of post-convulsive apnœa respiration fails to recommence normally, the patient's colour becomes livid and ashen, the pulse and heart-beat imperceptible, and the patient presents all the appearances of acute cardiac death. Treatment consists of immediate and vigorous artificial respiration followed by the intravenous injection

of coramine solution, 3-5 ccs. Response is always immediate, and to date no fatalities have been encountered. It has been the writer's practice always to discontinue the use of anoxia for patients who have once exhibited this form of vasomotor collapse.

Of minor complications, muscular pains, mandibular subluxation, headache, and transient mental confusion following the convulsion are quite commonly found. A not infrequent and rather troublesome minor complication is persistent left-sided cardiac pain, constantly localized to the apex region, and made worse by exercise. It is unaccompanied by physical signs of cardiac abnormality, and usually clears up within a week or so, with or without symptomatic treatment. It requires tactful handling and reassurance in the worrying, anxious type of patient, as it may readily lead to the idea in these patients that the treatment has inflicted organic damage of some kind upon the heart. Actual cardiac abnormalities pointing to organic derangement have never been found in any of the author's cases, and it would appear that much of the recent literature on this aspect of the treatment has been unnecessarily alarmist in tone.

Before leaving the subject of vascular disturbances in neurometabolic therapy, mention should be made of the pallor-bradycardia syndrome observed by the writer in a number of patients under insulin. This condition appears to be a milder equivalent of the acute collapse-syndrome just described for electroanoxia. It consists of a condition of persistent pallor combined with a bradycardia which may be as low as 48 per minute during the period of coma. This condition is uncommon, and generally occurs in patients of the typically pyknic habitus. It is a reliable sign of impending cardiac embarrassment, and the author always performs immediate intravenous termination if the sign persists for more than fifteen minutes. He regards patients who persistently exhibit this syndrome as poor therapeutic risks.

The question of cerebral complications in the form of permanent intellectual damage has been the subject of much discussion in the literature recently. As pointed out in a previous section of this chapter, the writer has yet to encounter a case showing intellectual deterioration which could be directly ascribed to the treatment rather than to the disease. As such intellectual impairment is found commonly in untreated cases showing mental deterioration, the latter supposition would appear to be much the most likely. Transient memory, impair-

ment and disorientation, however, is not uncommon as a temporary after-effect of electroanoxia ; it need cause no alarm, as it invariably clears up within a few hours of treatment.

(7) Causes of Failure in Neurometabolic Therapy

As electroanoxia and hypoglycæmia are specific for the dysoxic and dysglycic syndromes respectively, there is no reason why a favourable outcome should not be expected in all early cases, provided that treatment has been adequate and on correct lines. The most common causes of unexpected failure to obtain a good result will now be considered.

Undoubtedly one of the most common causes is undue timidity or delay in instituting treatment, especially in the acute forms of encephalopathy. As previously emphasized, it is useless to give electroanoxia two or three times weekly to cases of acute malignant dysoxia, as the cumulative effect of daily treatment is absolutely essential. The author has on one or two occasions in the worst cases administered treatment twice daily with a gratifying response and no untoward after-effects. The full course of nine to ten applications should always be given in these cases, and any signs of relapse treated promptly and energetically. The same remarks apply in the case of acute malignant dysglycia ; to adopt expectant treatment in these cases in the hope that a spontaneous remission may occur is always unjustified, since delay may mean the rapid destruction of neurones and association-tracts by the encephalopathic process, with consequent permanent residual deterioration. It should be remembered that early treatment in these cases can do much, but late treatment little, and the author is of the opinion that in the acute malignant forms under-treatment is likely to do more harm in the long run than over-treatment. The same remarks apply to ceasing treatment too early, another common cause of relapses and therapeutic failure.

It sometimes happens that an acute case shows in a disappointing and unexpected manner persistent residua and deterioration, in spite of early and energetic therapy. In these cases, a careful exploration of the previous history nearly always reveals either a previous acute attack with some degree of post-encephalopathic personality change, or suggestive evidence that, prior to the onset of the acute symptoms, the patient had been showing signs of a gradual and insidious personality-change for months

or even years previously ; in other words, the case was really one of the chronic and insidious type, the florid symptoms on admission being simply a culminating flare-up. This has been the explanation in several of the author's cases of unexplained and apparently causeless failure to respond favourably to treatment.

In any case which fails to make adequate progress, the possibility of concomitant physical disease, vitamin-deficiency, masked epileptic state, or other undetected organic condition should always be carefully considered.

Intercurrent physical disease necessitating temporary abandonment of treatment is always a potent factor in militating against a favourable neurometabolic response and in precipitating relapse. The acute infections are usually the commonest offenders in this respect, and the importance of careful attention to the general health in the form of adequate diet, vitamin-intake, and general hygiene will at once be evident.

Failure to attain coma in insulin-cases in spite of a carefully adjusted and adequate dosage of insulin is not uncommonly a factor which is found to militate against success. There are two common causes of this ; the first is sudden changes in the weather, a sudden spell of hot weather lowering the threshold of response to insulin and a sudden cold or wet spell the reverse. This factor should always be carefully considered when carrying out treatment in a climate as variable and uncertain as that of this country. In the case of hot weather, this appears to be due to the great increase of sweating and dehydration, with consequent greatly increased concentration of insulin in the blood. The second cause is surreptitious gorging by the patient on cakes, sweets, or other high-carbohydrate foods when unobserved during the intervals between treatments. The offending foods are usually obtained from other patients or visiting relatives, who do not realize the importance of limitation of the patient's diet. The remedy consists in adequate supervision of patients and their visitors during the intervals between treatments.

(8) Treatment of Residual Symptoms ; ancillary and other forms of Therapy

The two forms of residual symptoms which may be the legacy of an acute encephalopathic breakdown have already been described. No description of treatment is complete without

reference to these, of which the most important are the non-specific residua of functional nature.

General asthenia and lack of energy, accompanied by inability to concentrate are probably the most common symptoms of which convalescent patients complain. They should be treated with the usual tonics, adequate rest, reassurance, and graded occupational therapy. Benzedrine sulphate in doses of 10-15 mgms, given on rising in the morning and at midday is often beneficial in these cases. Care should be taken not to give the second dose later than the early part of the afternoon, or troublesome insomnia may result.

Mild degrees of memory-impairment and aprosexia are also common after-effects, and should be treated symptomatically along similar lines. At this stage of the convalescence, psychotherapy with reassurance and encouragement are of more importance than any form of drug-therapy; often patients are extremely distressed and anxious to find that their powers of memory and concentration are not as good as before their illness, and this applies expecially to those whose occupation is of an intellectual nature. Those of the anxious worrying type are only too prone to believe that their symptoms are due to organic brain-damage of some kind, and reassurance is most important here. It should be carefully explained to the patient that such symptoms are always present to some degree after any severe illness, whether mental or physical, that they are not due to organic brain-damage, and that it will only be a matter of time before they clear up and the patient is restored to his full previous working capacity and efficiency.

Insomnia of varying degree, sometimes accompanied by unpleasant dreams and hypnagogic hallucinations should always be treated thoroughly by means of hypnotics in full dosage, as described for the hystero-encephalopathic syndrome. Psychotherapy also is of great value here, since, as with the other symptoms, the worrying and obsessional type of patient is only too likely to put the worst possible interpretation on any abnormal sensations. The importance of insomnia as a precipitating factor of relapses has already been indicated.

In some patients of the anxious type, anxiety-symptoms may persist in some degree after the resolution of the encephalopathy, usually in the form of tension, irritability, and a varying degree of emotional instability. Sedation, a congenial occupation, and psychotherapy are useful in such cases; for the first-named,

luminal gr. ½ t.d.s. or a mixture containing either bromide alone in doses of gr. xx-xxx t.d.s., or combined with chloral gr. i-iii in each dose answer well in these cases. Benzedrine is not advisable in these cases, as it tends to accentuate the tension and irritability without producing any feeling of euphoria. The last-named drug appears to have its greatest use in the treatment of patients of the heavy, slow, and lethargic type of habitus.

Lack of insight alone, when not accompanied by other encephalopathic residua, is not in the writer's view necessarily a sign of ominous import. In many cases, it is due to the popular lay attitude towards mental illness. The ordinary person, particularly those of the uneducated classes, appear to have a fixed idea that a person can only be considered to be "mental" (*a*) if he is a low-grade mental defective, or (*b*) if he actually displays conduct of the type commonly associated in the lay mind with the music-hall comedian's idea of insanity. Anything less than this is simply called a "nervous breakdown," or an "attack of nerves"; such gross encephalopathic symptoms as delusions, hallucinosis, or stupor are usually described as "just his (or her) nerves, doctor." Apart from the gross degree of amnesia for the acute stage which is so common in remitted encephalopathics, it is not uncommon for the patient when questioned about his illness to consciously or unconsciously repress the memory of his experiences, rather than admit that he has been "mental," with all the sinister stigmata and implications which this word conveys to the layman's mind.

With regard to the amnesia, further mention is made of this as part of the mechanism of cure in the ensuing chapter. It is the writer's view that it is on the whole undesirable to try to force the patient to recollect and discuss painful and distressing experiences of the kind undergone during the course of an acute encephalopathic illness. This remark, of course, does not apply in the case of purely psychoneurotic patients, in whom anamnesis and recovery of repressed memories are among the most valuable and effective of therapeutic procedures.

The permanent encephalopathic residua, as distinct from the functional after-effects described above, offer a considerably more difficult problem. They are usually irrecoverable, and are, of course, due to permanent structural damage to the higher centres of the cortex and basal nuclei. The commonest of these are apathy, loss of initiative, thought-disorder, fixed delusions and hallucinations, affective changes, intellectual impairment,

and disturbances of conduct. In the milder forms, a suitable and congenial occupation under sheltered conditions, together with psychotherapy and appropriate medication, may enable the patient to make a reasonable adjustment and carry on a more or less useful and happy life. Those with the grosser residua usually become permanent inmates of mental hospitals, and offer problems of care and adjustment to the sheltered conditions of a mental hospital rather than of active therapy. In recent years, the operation of prefrontal leucotomy has come to hold out hope for some at any rate of these unfortunates, and the subject of psycho-surgery and its applications forms the subject-matter of a subsequent chapter of this book.

(9) Other forms of Treatment

The author is of the opinion that continuous narcosis has no place in the modern treatment of the metabolic encephalopathies. It has no specific effect on the metabolic disturbance, and has now been entirely superseded by the anoxic and hypoglycæmic methods of treatment. In acute malignant dysoxia and dysglycia it actually appears to accentuate the toxic and confusional features in many cases, while it is of no benefit in the more chronic types.

The use of benzedrine has likewise proved disappointing, It is entirely without effect in depressed and retarded dysoxics, as it is in the pure affective forms. Its only application is in the treatment of the residual asthenia and loss of confidence in convalescent patients. Many agitated and tense dysoxics are definitely made worse by administration of the drug, while in excitable and impulsive patients it appears to exacerbate the aggressive and impulsive tendencies.

The role of sedatives and hypnotics has already been indicated. The author prefers to avoid the use of paraldehyde and sulphonal for patients undergoing electroanoxia, since these drugs tend to raise the convulsive threshold by reason of their slow and prolonged action, if they are administered on the night before treatment. Treatment-baths and intensive sedation can be entirely eliminated even in the worst cases of excitement as the result of use of the electroanoxic and hypoglycæmic therapies, and the author has never yet had to have recourse to these measures. In violent and resistive patients who are receiving electroanoxia and require sedative premedication, the author

has found morphine and hyoscine, gr. 1/4 and 1/75 respectively, to be best, as these drugs do not tend to raise the convulsive threshold appreciably.

Psychotherapeutic measures are of limited use in the treatment of the metabolic encephalopathies, since the essentially organic nature of these conditions and the almost invariable lack of insight are insuperable obstacles to the success of psychotherapeutic measures without the preliminary exhibition of neurometabolic therapy. They have their greatest use in the treatment of the residual symptoms in the convalescent period, as already described. Psychotherapy is also of particular value in the handling of the recovered patient and in reassurance, especially with regard to such questions as subsequent marriage, employment and sexual hygiene.

Of alternative methods of inducing anoxia, pharmacological agents such as cardiazol, triazol, and picrotoxin have now been entirely superseded by the electrical technique. The disadvantages of convulsant drugs—apprehension, damage to veins, and unpleasant after-effects are almost entirely eliminated by the use of the electrical method, and drug-induced convulsions appear to have no appreciable therapeutic superiority over electrically-induced anoxia. The high cost of these convulsant drugs as compared with that of electrical methods and the difficulties of supply under present conditions are also considerable drawbacks to their use on a large scale as usually employed in hospital-practice.

The histamine-insulin method advocated by Hill has not gained general acceptance in the therapy of the metabolic brain-disorders. The writer has so far found it to be entirely ineffective for both the dysoxic and dysglycic forms ; the only physiological effects of this treatment are intense autonomic stimulation and vascular dilatation, the cerebral anoxia and break of consciousness which are the two most important mechanisms of cure not being produced in this treatment, which explains its lack of therapeutic efficacy.

The author has had no experience of the use of synthetic hormonal preparations, as suggested recently by Hemphill and others. Convincing evidence of their efficacy as curative agents, as of gonad-deficiency as a causal factor in metabolic encephalopathy, is as yet lacking ; moreover, the high cost of these preparations, especially the synthetic androgens, constitutes a serious obstacle to their general use in mental hospital-practice.

The use of thyroid in large doses, however, does appear to be of benefit in certain types of dysoxia, in which the clinical features are hebetude and stupor combined with an obese, heavy habitus suggestive of mild thyroid-deficiency. It appears to be of most value when given in dosage of gr. iii three times daily, preferably in combination with electroanoxia; many of these patients tolerate much larger doses without ill-effect. Its main range of usefulness has been shown by Gjessing to be in the treatment of the rare form of dysoxia known as periodic katatonia, in which there is a disturbance of nitrogen—metabolism associated with the katatonic phases.

Narcoanalysis is chiefly of value as a diagnostic test in cases of acute confusion and stupor, and for temporarily rendering an inaccessible patient co-operative, in order to unmask symptoms by abolishing the stupor, so as to permit of exploration of the history and phantasy-life of the patient. It is also of some value as a prognostic guide, since it has been found that patients who make a good response to narco-analysis are usually those who do best under neurometabolic therapy, whereas a poor narco-analytic response in general is indicative of a bad prognosis.

(10) The Medico-Legal Aspects of Neurometabolic Therapy

The neurometabolic therapies involve some important medico-legal considerations, without mention of which this chapter would be incomplete. The most important of these are the problem of the non-co-operative patient, and the consent of the patient's relatives for treatment.

Hypoglycæmia and anoxia are generally considered for medico-legal purposes as involving the same risks as general anæsthesia, although the actual mortality in proper hands is extremely small. In civilian practice it has always been the rule in hospitals and clinics where it is carried out to obtain the consent of the patient's relatives before instituting such treatment. During the latter part of the war, a similar rule was introduced by the Medical Department of the War Office in dealing with military cases. The author is of the opinion that the psychiatrist should always safeguard himself by adopting such a procedure; if possible, the patient's relatives should always be interviewed personally, and the seriousness and possible consequences of the patient's illness explained, without, however, taking an unduly pessimistic or alarmist view of the case. It should be pointed out that, although in a proportion of such cases spontaneous remission

may eventually occur, such a fortunate outcome cannot be relied upon, and that neurometabolic therapy offers by far the best chance of ultimate recovery. It should always be stressed that in a normal and physically healthy adult the actual risks involved are very slight, and certainly much less than those of allowing the case to go untreated. In the case of the milder forms, such as the derealization-states and mild types of depression, in which insight and co-operation on the part of the patient are unimpaired, the consent of the patient himself in writing may be sufficient ; this applies particularly in cases where the patient does not wish his relatives to know the true nature of his condition, and feels that they might be unduly anxious and distressed if they knew he was in a mental hospital as a voluntary patient. In cases where the patient is considered to be unable to appreciate the nature of his illness and the projected treatment, and there is any likelihood of opposition to such treatment on the part of the relatives, their consent should, if possible, always be obtained. During his time as a military psychiatrist, the writer saw one such case in which a dysglycic patient was given hypoglycæmic therapy despite the objections of his relatives, who were violently prejudiced against the use of all forms of physical therapy in mental disorders. The patient in question unfortunately developed irreversible coma and died without recovering consciousness ; at the subsequent inquest, the medical officer in charge of the case came in for virulent abuse and attack by the patient's relatives.

The question of consent is also especially important when dealing with cases in which there is any serious co-existing physical disease, such as renal or cardiovascular conditions. The relatives should always be warned that neurometabolic therapy carries a considerably greater risk under these conditions, and a special form of consent may be advisable under these circumstances.

The one exception to these rules is the fulminating type of malignant encephalopathy, which demands immediate and energetic treatment as an acute medical emergency. As already stressed in these cases, failure to effect such treatment may mean early and irreparable damage to the cerebral tissues, and this aspect should always be considered when there is a possibility of any undue delay in obtaining the relatives' consent by reason of distance or other difficulties of communication. In military practice, this applies particularly to the case of patients who are under treatment in hospitals overseas.

The problem of the non-co-operative patient is often a difficult one, since it sometimes raises the question of the rightness or otherwise of compelling a patient to have treatment against his will by physical means. In civilian practice, compulsion is not used in the case of voluntary patients ; in the army, the rule has recently been laid down that compulsion must not be used in the event of a patient's refusal of treatment, even though the consent of his relatives has been obtained.

The confused, inaccessible, or otherwise avolitional patient who is resistive to treatment presents little difficulty in this respect. The most troublesome cases are the more chronic delusional types, whose mental condition does not prevent them from expressing volition, and who not uncommonly have a very real dread of the treatment, and adopt a hostile attitude towards any attempt to help them. This is often partly due to lack of insight, and partly to the patient's unwillingness to be forcibly separated from the phantasy-life which he has built up as a defence against unbearable realities, and which is, from his own point of view, a perfectly satisfactory solution to his emotional problems. Such patients can sometimes be dealt with by persuasion and reassurance, and if these fail, by premedication. Often, however, all these methods are unavailing, and the scrimmage which invariably accompanies any attempt to enforce treatment may have a disastrous and infectious influence on other patients, apart from being an extremely disagreeable and time-wasting experience. This unfortunate state of affairs is in addition often complicated by the attitude of importunate relatives, who insist that the patient must have all the "latest new treatment," whether he likes it or not.

The writer is of the opinion that compulsion should never be employed in dealing with this type of case. It is not only unnecessarily cruel, but tends to render the patient even more hostile and resentful in his relationship with his medical attendant, the doctor-patient relationship suffering irreparably thereby. The advisability of forcibly tearing a partially-adjusted encephalopathic away from his phantasy-life has been questioned by many psychiatrists of the more conservative school, and on this point the writer finds himself generally in agreement with this school of thought. He feels that the correct attitude in these cases should always be that the doctor is only an adviser, and that the patient, whether certified or otherwise, should always be free to

accept or reject his advice as he wishes. The treatment of such cases should be occupational and psychotherapeutic, and directed towards helping the patient to lead a reasonably happy and useful life and to make the best of his partial adjustment to reality. To satisfy the demands of relatives and make them feel that something is being done for the patient, some less drastic therapy, such as the histamine-insulin technique, may be employed in these cases as a placebo. No hard and fast rule can be laid down for dealing with these difficult cases, and each has to be dealt with according to its particular merits and circumstances. Reference has already been made in this connection to the possible dangers of over-enthusiastic use of the neurometabolic therapies in the partially-recovered encephalopathic patient.

(11) Statistical Results of Neurometabolic Therapy

In a series of 100 early dysoxics treated by electroanoxia during the author's experience as a military psychiatrist, the following results were obtained :—

Total number treated	100		
Discharged recovered	74	=	74%
,, improved	23	=	23%
,, unimproved	3	=	3%

Of a series of 61 early dysglycics treated by hypoglycæmia, the results were as follows :—

Total number treated	61		
Discharged recovered	35	=	57.4%
,, improved	16	=	26.2%
,, unimproved	10	=	16.4%

It will be evident that these results are on the whole considerably better than those usually obtained in civilian practice, and that the series of dysoxic cases showed a substantially better remission-rate than the dysglycic series. This was due to the fact that the latter included a considerable number of the more chronic paranoid type of later age-incidence.

The criteria for complete remission were considered to be total abolition of sensory phenomena, restoration of the normal affective reaction, absence of associational and thinking-disorder, restoration of normal conduct and interests, and the presence of a reasonable degree of insight.

(12) Note on the Apparatus and Practical Technique of Electroanoxia

The problems involved in the design and construction of a simple and efficient apparatus for the administration of electro-anoxic therapy have recently been the subject of considerable discussion in psychiatric journals, the most recent and constructive article on the subject being that of Caplan (*Journal of Mental Science*, April 1945).

During the last five years the author's experience has been chiefly with the MacPhail-Strauss and the Ediswan types of machine, each of which has its own particular advantages and drawbacks.

The Ediswan apparatus is probably the simplest and most stoutly constructed machine for all-round purposes on the market to-day. It stands up well to the inevitable amount of rough handling to which any electrical apparatus in use in a large hospital is liable to be subjected, and has the great advantage of extreme simplicity of layout and a minimum of "gadgets." There is only one fuse, located in the mains circuit, and the time-switch is of the electrical motor-driven variety. It weighs less than thirty pounds, and is easily portable. Its principal disadvantage is that it employs a resistance instead of a transformer to step down the voltage, so that there is direct connection between the mains and the patient; this arrangement is thus not so safe as is the transformer type. Also the heating-up of the resistance-wire after the machine has been running for a short time causes the top casing to become quite hot to the touch, and necessitates the presence of ventilation-holes; thus there is always the liability of saline solution being accidentally dropped down the holes during use, with possibly disastrous effects should it run down inside and come into contact with the resistance or its connections. For experimental work in which very accurate readings of voltage and head-resistance are required, this type is much less accurate than the transformer type, although perfectly satisfactory for ordinary out-patient or in-patient use. Another disadvantage is that the time-switch, which employs moving parts, is bound to suffer a certain degree of wear and tear after the apparatus has had a period of prolonged use.

The MacPhail-Strauss machine is a considerably more elaborate and refined affair. It differs from the Ediswan in the following respects; it incorporates a transformer for voltage-

reduction, has a separate mains current calibrating arrangement, and the dials for calculating head-resistance and voltage-adjustment for the shock-dose are separate, and not incorporated into one, as in the Ediswan machine. The latest model in addition employs a cathode-ray indicator for the resistance and calibration, and a fixed time-adjustment of 0.5 second. There are two fuses of different amperage, one in the mains and one in the resistance-circuit. This type of apparatus gives much greater accuracy in the voltage and head-resistance readings.

In the writer's experience, the MacPhail-Strauss has only one real advantage over the simpler types—namely, the transformer in place of the resistance, which ensures absolute safety and eliminates the over-heating complication. Otherwise, its disadvantages outweigh its good points altogether. It is far too elaborate and complicated for general routine use, is liable to constant breakdowns for this reason, and has an aggravating habit of blowing a fuse on the slightest provocation. Unlike the Ediswan, it cannot be easily and quickly repaired by an ordinary electrical technician.

The principal weakness of all machines at present on the market is the connection between the electrodes and the machine-to-patient wires, which are always liable to become corroded after a short time by the action of the saline solution, with consequent gradually increasing resistance and final breaking-off of the connection. This difficulty has never yet been satisfactorily overcome.

The most satisfactory form of headband is that supplied with the Ediswan machine. It consists of a single stout rubber band, fastened in front by a clip and studs, the electrodes being two lead discs with holes for the terminals of the machine-to-patient wires; for the actual contact-surface, sponge or sorbo-rubber pads covered with gauze are secured over the discs by means of tightly-fitting bakelite rings encircling the edges of the discs. The discs are attached so that they can be slid along the band to allow for any size and shape of head, the clamp-fastening in front also being adjustable to allow for size; this ensures a tight contact, and is a strong and durable form of headband. The form supplied with the MacPhail-Strauss consists of a broad, thin rubber band with a series of holes to allow for adjustment to different sizes of head, the whole being secured by means of studs passed through the holes. The electrodes are simply flat, thin metal plates unattached to the headband, and are secured when

in use by placing them over the prefrontal area and strapping them on wrapped in gauze by means of the headband. This form takes longer to apply than the Ediswan form, and the headband, being only of thin rubber, is always liable to perish or tear through if applied to tightly.

All the present-day models of electro-convulsant apparatus suffer from being too complex and elaborate, with an unnecessary number of " gadgets " and consequent weaknesses and tendency to break down readily when in use. The possible improvements suggested by the writer's experience are as follows.

The resistance-measuring circuit could be dispensed with altogether, since it is quite unnecessary, and considerable saving in weight and bulk of the apparatus can be effected thereby. Preliminary measurement of the head-resistance is quite unnecessary in practice, for the following reasons ; the normal head-resistance values have been found to vary in different subjects by as much as 1,000 per cent. (Caplan) ; the resistance-reading is no indication of the convulsive threshold and voltage required ; the tissues of the human head do not obey Ohm's law of electrical resistance, and in any case resistance-values obtained with a direct current through an ordinary potentiometer are always inaccurate. The head-resistance is also dependent on such variable quantities as the state of cleanliness (or otherwise) of the skin, and the presence or absence of hair over the area to which the electrodes are applied. There is no satisfactory method for determining the voltage and time-values required to produce a convulsion, apart from that of trial and error.

The calibration-circuit can also be eliminated, as in the Ediswan and other simpler forms of apparatus ; it is really not essential, as the amount of current-fluctuation in ordinary A.C. mains is very small.

The transformer type of voltage-reduction mechanism should in the writer's opinion, be adopted in all cases. Its advantages over the resistance-wire type have already been enumerated.

For extreme simplicity, the time-variation mechanism could also be cut out, as in the latest MacPhail-Strauss model, the voltage only being adjustable. If a variable time-setting is required, the motor-driven type as in the Ediswan appears to be the most suitable. Its possible disadvantages have already been indicated ; on the other hand, it has the advantages of strength and durability, since the machine ordinarily is only kept running for short periods at a stretch, so that the mechanism is only likely to show signs

of wear after a very long period of use. The electronic type is open to the objection that its life as compared with the motor-driven switch is short, as it tends to burn out after a considerable period of use.

The problem of a satisfactory connection between the patient-leads and electrode could be simplified by adopting the device suggested in the diagram on the opposite page. It is a modified form of the Ediswan headband and electrode, with the modification that the connection, instead of plugging directly into the lead disc, is carried on a flexible brass or copper strip about six inches long soldered or screwed into the thickness of the disc, the lead being soldered into the free end of the strip. In this way the actual connection is kept clear of contact with any saline solution which is squeezed out of the electrode-pads, so that corrosion and breaking of the connection is avoided. A flexible metal strip rather than a rigid rod is employed, since it bends easily and thus cannot accidentally be fractured as a result of sudden violent movements of the patient's head during the convulsion.

The ultimate simplified form of electroanoxic apparatus suggested would therefore be one built on the same plan as the Ediswan machine, with the following modifications :—

(1) Abolition of the resistance-meter and calibration-circuit.

(2) Voltage step-down resistance replaced by a transformer, giving readings from 50 to 150 volts, with tappings at every 5 volts.

(3) Modified anti-corrosion electrodes as described above.

SUGGESTED DESIGN FOR IMPROVED ELECTRODES AND TERMINALS FOR ELECTROANOXIC THERAPY.

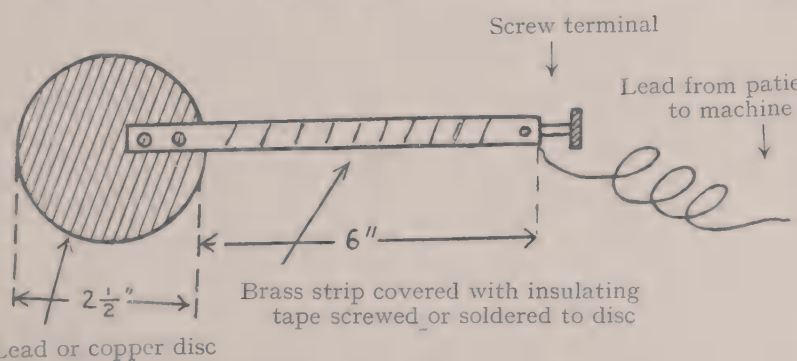

Fig. 1. Modified Electrode (Ediswan Type).

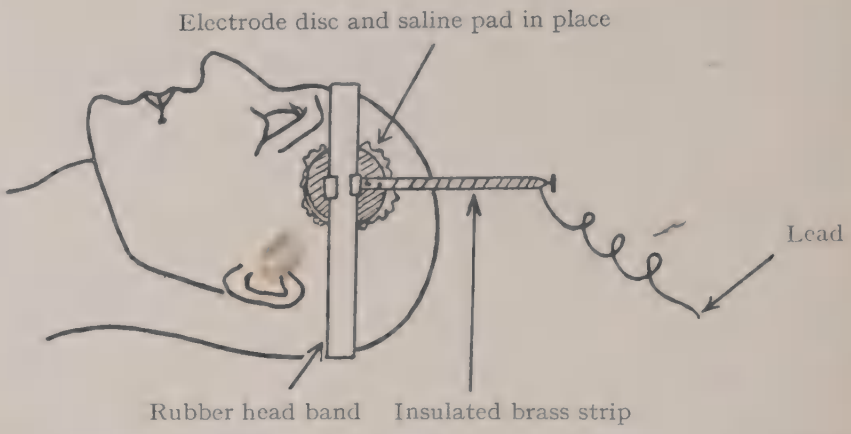

Fig. 2. SHOWING ELECTRODE IN PLACE, AND METHOD OF KEEPING JOIN CLEAR OF SALINE PAD.

CHAPTER XIII

THE BIOCHEMISTRY AND PHYSIOLOGY OF NEUROMETABOLIC THERAPY

(1) The Nature of Neurometabolic Therapy ; History

Before proceeding to a discussion of the theoretical basis of and biochemical changes involved in these forms of treatment, it may be as well to define first what is meant by the term " neurometabolic therapy " ; since, largely as the result of sensational journalism and certain medical writers whose pens have been guided by emotional feeling rather than sound judgment, some highly distorted and erroneous ideas have grown up regarding this form of treatment.

Neurometabolic therapy is by no means an innovation. As far back as the early years of the last century, electrical methods were used in the treatment of mental disorders, in addition to the cruder methods such as whirling-chairs and sudden immersion of the patient in cold water. Such techniques probably owed what success they had to the powerful autonomic stimulation produced thereby ; thus, the older physicians, although ignorant of the physiological mechanisms involved in metabolic brain-disease, actually employed a form of therapy possessing in some respects a perfectly sound empirical basis. This question of autonomic stimulation and its importance in the mechanism of cure will be further discussed in the subsequent sections of this chapter.

As time went on, somewhat more refined methods were introduced, such as the induction of protein-shock and artificial fever by means of injections of colloidal sulphur, sterile milk, or T.A.B. vaccine. These methods were unsuccessful because no direct and potent action on the cerebral glucose-oxygen metabolism and autonomic centres was achieved thereby, and it was not until the last two decades that any real advance in this form of therapy was effected.

As with many other great discoveries in medicine, the principles and technique of the neurometabolic therapies were a more or less accidental discovery, their use at first being purely empirical. It was, in fact, originally based on a fallacious theory

—namely, that a biological antagonism existed between the dysoxic-dysglycic syndrome and the convulsive states. It is only within the last few years, in the course of which our knowledge of the cerebral respiration-mechanisms has been greatly extended, that the rationale and physiological processes underlying the anoxic and hypoglycæmic treatments have been brought to light.

Convulsive—or to use a more accurate term, anoxic therapy was first introduced in 1934 by Meduna, who based his treatment on the hypothetical biological antagonism between epilepsy and the metabolic encephalopathies. His original technique for the induction of anoxic convulsions was the intramuscular injection of camphor in oil, a procedure attended by many disadvantages, including pain at the site of injection and multiple delayed fits. Later, this method was abandoned in favour of the intravenous use of cardiazol and the intramuscular injection of triazol. Insulin, or hypoglycæmic therapy, was introduced by Sakel in the early 1930's, as the result of his observations of the beneficial effect of hypoglycæmia on the mental symptoms found in the abstention-syndrome of morphine-addicts; as a result of these observations, he proceeded to test the effect in states of dysglycic excitement, and the therapeutic effects were so striking that this form of treatment became eventually established as a recognized procedure in the therapy of these conditions. A further great advance was the introduction by Cerletti and Bini in 1938 of the electrical method of induction of anoxic convulsions. This eliminated the use of analeptic drugs, with all their accompanying drawbacks, such as thrombosis of veins, multiple fits, post-convulsive headache and vomiting, and preconvulsive aura with consequent dread and apprehension on the part of the patient.

Neurometabolic therapy, then, may be defined as the use of a therapeutic agent to produce a sudden chemical and metabolic change in the biochemical activities of the whole body, and particularly in the cerebral respiration-mechanisms; the alteration being effected directly through a change in the oxygen-glucose metabolism of the brain, and indirectly through a concomitant stimulation of the autonomic nervous system. The therapeutic agent employed may be either chemical, as in hypoglycæmia, or physical, as in electroanoxia. Two principal types of neuro-metabolic therapy may be distinguished; anoxic, or convulsive therapy, in which the primary effect is upon the oxidising cells and cerebral oxidation-processes, and hypoglycæmic therapy,

in which the main attack falls upon the glycolyzing cells and glycolyzation processes. It should, of course, be borne in mind that certain of the biochemical changes, such as sympathetic stimulation, hypoxia, and hypoglycæmia, are common to both methods as will be seen presently, and that the two methods are thus not in any way mutually exclusive.

(2) General Biochemical Changes in Hypoglycæmia and Anoxia

The underlying mechanism of the neurometabolic therapies is a profound alteration of the respiratory processes of the entire central nervous system. Four principal changes are found, which are common to both the anoxic and hypoglycæmic processes. These are a profound disturbance of consciousness, sudden in electroanoxia, and gradual in hypoglycæmia; an extremely powerful stimulation of the entire autonomic system; cerebral anoxæmia, and cerebral hypoglycæmia. In addition, characteristic changes are produced in the electroencephalogram, conditioned reflexes, general behaviour, and central nervous system. The net effect is thus a profound change in the physico-chemical milieu not only of the nervous system but of the whole body.

The cerebral effects depend upon the fact that brain-tissue is peculiar in being far more sensitive to oxygen and carbohydrate-lack than any other of the body-tissues, and that the most highly-developed portions of the neuraxis are much more sensitive than the lower and less highly-developed regions. Thus, the grey matter of the cerebral and cerebellar cortices, which have the greatest oxygen-consumption of any part of the brain, are first and principally affected by anoxia and hypoglycæmia. The oxidative activities of the different kinds of brain-tissue can thus be interfered with in three ways, by a gross lack of oxygen, by deficiency of the available carbohydrate, or by a specific effect on the intermediate cellular oxidation-processes.

The general effects on cerebral tissue-respiration may be briefly summarized as follows. The excitability of the cortical tissue is dependent on the blood-sugar level as well as on the oxygen-tension, these being synergistic. Thus, the effect of anoxia on the brain-potentials is increased by hypoglycæmia, while the effects of hypoglycæmia can be counteracted by inhalation of 100 per cent. oxygen. It is found that, in cerebral anoxia, although the functions of the somatic nervous system are

depressed, the tone and excitability of the sympathetic and parasympathetic systems are actually increased.

As regards the electroencephalographic response, the *a*-wave frequencies are increased by agents which produce an increase of metabolism, such as thyroid and benzedrine, but decreased by hypoglycæmia and narcotics which lower the metabolic rate.

It will be evident from the foregoing remarks that the immediate effect of both anoxia and hypoglycæmia on the central nervous system is a general depression of metabolism, with at the same time a marked increase in activity of the autonomic system; this is followed on cessation of the treatment by a reactionary increase of cerebral metabolism in the direction of normality, with simultaneous cessation of autonomic hyperactivity. This is a well-known observation in pharmacology, and is exemplified by such experimental procedures as the injection of a vasoconstrictor drug which produces an immediate rise in blood-pressure, to be followed by a compensatory fall as soon as the effect of the drug has worn off.

(3) The Biochemistry of Electroanoxia

The most striking change in anoxic therapy is undoubtedly the marked degree of anoxæmia produced. Clinically it is seen in the intense cyanosis, especially of the face and neck, which lasts on the average from one-and-a-half to two minutes, and biochemically in a marked decrease in the oxygen-saturation of the blood, which may fall to only 42 per cent. of its normal level during the convulsion.

There is a profound fall in the PH of the blood, which may reach the lowest level compatible with life. This is probably due to the enormous and sudden output of lactic acid generated by the violence and intensity of the muscular contractions.

The blood-sugar is greatly decreased during the convulsion, and this is followed by a rapid increase to a level exceeding the normal renal threshold after the end of the clonic convulsive phase.

The serum-proteins, cholesterol, phospholipids, and inorganic phosphorus are increased above the resting level to 100 per cent. and return together with the blood-sugar to their previous level within two-and-a-half hours after the application of the convulsive shock.

The blood chlorides remain within normal limits, although there is an actual increase during the time of the convulsion.

In the C.S.F. the immediate effect is lowering of the albumin-globulin ratio. After one or two weeks of treatment, or about three to six convulsions, the albumin and albumin-globulin ratio are found to be increased, because the total amount of globulin is decreased. At the same time there are alterations in the volume of cerebrospinal fluid and permeability of the blood-brain barrier, which changes are also found in hypoglycæmia. The C.S.F. pressure undergoes a sudden increase with the onset of the convulsion.

In the cardiovascular system, there is first a rise, followed by a fall, in blood-pressure, with tachycardia followed by slowing of the pulse-rate. Generalized vasodilatation with suffusion of the face and conjunctivæ are apparent immediately following the convulsion, and the cerebral vessels undergo a similar change as shown by observation of the retinal vascular network by means of the ophthalmoscope. This sudden dilatation of the cerebral vessels with increased permeability and blood-flow to the brain-tissues is probably an important factor in correcting the abnormal metabolic activities of the affected neurones. Leucocytosis is found for several hours after the application of the convulsion.

The effect of the shock on the respiratory centre is one of immediate inhibition followed by stimulation. Immediately after cessation of the clonic phase, there is an apnœic interval lasting up to half-a-minute or more, followed by a series of forcible and prolonged respirations in which the accessory muscles are brought into play. This temporary inhibition of respiration followed by increased activity aids in inducing the cerebral anoxæmia, and probably acts as a powerful stimulant to the cerebral metabolic activities.

The autonomic changes consist of a powerful combined sympathetic and parasympathetic stimulation, and are evident in the vasodilatation, tachycardia, blood-pressure changes, voiding of urine, salivation, and sometimes erection and ejaculation of semen.

The electroencephalographic changes resemble those of the true epileptic fit, the area of focal discharge approximating to that of the resting delta foci in idiopathic epilepsy, so that during the convulsion the characteristic epileptic "spikes" are seen in the E.E.G. tracing. During the course of treatment there is an increase in the abnormalities noted in the E.E.G.

The changes in the C.N.S. are confined entirely to the motor system. They may be divided into those of the convulsive and

post-convulsive phases. The convulsion in electroanoxia differs in no way from that of the epileptic, except that on application of the current unconsciousness is instantaneous, preconvulsive aura being absent, and the fit commences with a violent jerk at the moment of passing the current. The onset of the convulsion proper may be almost immediate, or there may be a latent interval of up to a minute between the application of the shock and the commencement of the tonic stage. The post-convulsive nervous signs are those of stimulation of the premotor cortex, and include pupillary dilatation, conjugate turning of the head and eyes to one side, chewing and licking movements of the mouth and jaws, grasping and threshing movements of the limbs, and extensor plantar responses. If the current has been of insufficient strength to produce a convulsion, a subconvulsive reaction resembling *petit mal* results, or a typical unilateral convulsion of Jacksonian type may be produced.

The most important metabolic change resulting from the anoxic convulsion is, of course, that which takes place in the respiration of the cerebral tissues. As we have seen, the most striking result of the convulsion is the marked reduction of the oxygen-supply to the brain during the convulsive phase. This is due to two factors, interference with the respiratory movements preventing oxygenation of the blood in its passage through the lungs, and the sudden enormous increase of activity of the brain-cells. The result is that, even were the oxygen-supply to the brain normal, it would be insufficient to meet the greatly increased demands of the active tissues. The oxygen-saturation, as previously stated, falls to 42 per cent. of its normal value, and this also occurs when the convulsion is modified by the use of paralysant drugs, such as curare or quinine methochloride. This reduction is also produced by cardiazol, insulin, and potassium cyanide when no fit occurs. A still greater reduction is effected by the inhalation of nitrogen or nitrous oxide, although this method of inducing anoxia is clinically less effective than the electroanoxic fit.

The reduced oxygen-supply to the brain results in an enormous increase of lactic acid content up to seven times the normal value. There is no diminution of the cerebral circulation, but actually an increase after the convulsive phase has ended.

The fall in oxygen-tension which occurs simultaneously with the convulsion begins several seconds before the first electrical

sign appears in the cortical potentials, and reaches its lowest value approximately half-a-minute after the last large potential seizure. The fall in oxygen-tension amounts to more than a third or up to three-quarters of that obtainable by means of nitrogen-inhalation. The fall in oxygen-tension thus occurs not only before the onset of the electrical seizure, but long before there is any circulatory change, the only alteration in the cerebral circulation being seen is the increase which would produce the rise in oxygen-tension. It will thus be evident that the initial fall in oxygen-tension indicates a rise in oxygen-consumption of the brain-cells long before it reaches a degree of hyperexcitability sufficiently great to produce a convulsion.

The actual electrical change itself is of the typically epileptic form, with a sudden burst of spiked waves of high amplitude. There is usually a short period of electrical hyperactivity of the brain-cells as shown by the E.E.G. after the convulsion is over.

The motor phenomena are much more pronounced in electroanoxia than in hypoglycæmia, whereas in the latter condition the depression after motor activity is much deeper. In contrast to the hypoglycæmic syndrome, which is predominantly a release-phenomenon, the electroanoxic syndrome is primarily a sudden and powerful stimulation of the entire neuraxis.

(4) The Biochemistry of Hypoglycæmia

Hypoglycæmia differs from electroanoxia in the following respects. The whole process has a much slower and more gradual evolution, its duration extending over a period of hours as compared with the few minutes of the electroanoxic cycle ; the profound degree of cyanosis and anoxæmia seen in anoxia do not occur ; the autonomic response is of much longer duration and better marked than in anoxia ; and the effect on the blood-sugar is correspondingly greater in hypoglycæmia.

In addition to its specific property in lowering the blood-sugar, insulin in neurometabolic dosage has the properties of a narcotic and deliriant, a central nervous stimulant and convulsant, and a specific stimulant of the autonomic system. In hypoglycæmic therapy, the first two effects are seen in the somnolence, confusion, and dulling of the mental faculties, and the second in the motor and convulsive phenomena which occur at various stages in the course of the coma. The third effect, that of autonomic stimulation, will be referred to in greater detail later.

The biochemical changes produced may be divided into those found in the general body-metabolism, as shown by the alterations in the blood-chemistry, and the specific changes in the respiratory activities of the central nervous system.

The most characteristic change in the blood-chemistry is, of course, the hypoglycæmia, which reaches its maximum one-and-a-half to two hours following the injection, the blood-sugar falling to approximately 40-30 mgms. per cent. The sugar level of the venous blood averages generally below 25 mgms. per cent. This lowest value coincides with the actual onset of the coma, and not with the period of deepest coma, and from this point onwards the blood-sugar rises progressively. This fact is important from the practical point of view, since it follows that it is much more difficult to rouse a patient by the oral method of glucose-administration at the time of onset of the coma than at a later stage, when the coma has lasted an hour or more and the blood-sugar has started on its upward curve.

The blood-phosphate is diminished by 25 per cent. of the normal value, and this simultaneous lowering of blood-phosphate and glucose illustrates the well-known interconnection between phosphate and glucose-metabolism.

The blood-chlorides are lowered slightly, the calcium, potassium, and cholesterol values being inconstant. There is a rise in the serum-lipoids, with the exception of cholesterol; as noted previously, these have usually a lowered value in the untreated dysglycic patient. This rise in serum-lipoids corresponds with a favourable clinical result from the treatment. The PH is shifted to the alkaline side.

The blood-pressure changes are similar to those described for anoxia. The blood-cytology shows a mild leucopenia during the first hour of hypoglycæmia, followed by a leucocytosis in the ensuing stages—the so-called "sympatheticotonic blood-picture," which is possibly due to a compensatory endogenous liberation of adrenaline. The choline-esterase activity of the serum is increased during the period of coma.

The albumen-globulin ratio is altered during hypoglycæmia, the globulin being increased and the albumen lowered; on discontinuing the treatment, the albumen-globulin ratio rises and the globulin decreases.

In the C.S.F. the sugar-content is lowered correspondingly with that of the blood, the level being usually 5-10 mgms. higher

than that of the blood. The albumen-globulin ratio undergoes the same changes as in anoxic therapy.

The electroencephalographic changes consist of a decrease or disappearance of the α-waves, and increase in the δ-index. The α-waves reappear after administration of glucose. It has been noted that improvement in the clinical symptomatology coincides with lowering of the δ-index.

The autonomic phenomena of neurometabolic therapy are seen at their best in hypoglycæmia. They consist of a mixed effect due to simultaneous stimulation of both the sympathetic and parasympathetic systems. In many cases however, the sympathetic and parasympathetic symptoms alternate in a regular sequence, the order being first parasympathetic stimulation in the early stages of the narcosis, followed by sympathetic excitation, and finally parasympathetic preponderance in the later and deepest stages of coma. The adrenalin content of the blood is always raised during hypoglycæmia. The parasympathetic features, which commence within the first hour after injection. consist of drowsiness, profuse sweating, dilatation of the cutaneous vessels and constriction of the pupils, voiding of urine, profuse ropy salivation and increased flow of gastric juice, and slowing of the heart-rate. To this syndrome in the early days of insulin-therapy Sakel gave the name of " wet shock " in his original monograph.

The sympathetic syndrome, originally named by Sakel " dry shock," sets in usually about two to three hours after the injection and often immediately precedes the moment of passing from sleep into coma. It shows itself by generalized pallor due to cutaneous vasoconstriction, acceleration of the pulse, pupillary dilatation and exophthalmos, due to stimulation of Muller's muscle as in thyrotoxicosis. This last sign is particularly characteristic, producing a peculiar staring appearance and " pop-eyed " expression which usually marks the actual moment of onset of coma ; it is, indeed, in the author's experience the most reliable sign of the onset of coma.

In some patients, the parasympathetic syndrome may be almost absent, the sympathetic features predominating throughout, so that the patient passes straight over the initial stage of drowsiness through the " dry " stage of coma, without displaying the sweating, salivation, and other symptoms of parasympathetic excitation. In these cases, a hypoglycæmic convulsion is particularly liable to occur during the first two to three hours of the

hypoglycæmia. In other patients, the reverse is the case, parasympathetic features alone being present throughout.

In the central nervous system, the narcotic effect of insulin is especially well seen in the early stages, with depression of the higher and release of the lower centres, the whole picture often bearing a strong resemblance to that of the first stage in general anæsthesia. Mental confusion, somnolence alternating with restlessness, groaning, noisy and excited periods with shouting and singing, and struggling, are frequently seen ; later, concomitant with the sympathetic signs, the features of stimulation of the motor and premotor areas of the cortex appear. These commence with fine fibrillary spasms of the orbicularis and facial muscles, progressing to generalized clonic spasms of epileptiform type which tend to become more and more violent ; these spasms may then gradually subside, or a typical epileptiform seizure may occur. The Babinski sign and grasp-reflexes with generalized hyper-reflexia are apparent at this stage. Later, torsion-spasms with hypertonicity and opisthotonus set in, the limbs being held in a position resembling that of decerebrate rigidity. These last-mentioned signs indicate that the deepest degree of coma compatible with safety has been reached. In the last stage, deep coma with flaccidity, abolition of the corneal reflex, incontinence, and reappearance of the parasympathetic signs is found.

The hypoglycæmic convulsion differs in no respect from that of electroanoxia. It may occur quite suddenly, or follow a period of clonic spasms. It is often found that immediately following the fit, or following a prolonged period of twitching without convulsion, the patient may awake spontaneously. This is probably due to a sudden liberation of adrenaline with mobilization of the remaining stored glycogen in the liver, as a result of the intense muscular activity.

The respiration in coma of average depth is slow and deep, resembling that of a normal deep sleep. Cyanosis and respiratory embarrassment do not normally occur ; if they do, it is a warning sign of impending circulatory failure or respiratory obstruction due to spasm of the glottis, and constitutes an indication for immediate termination of the coma. This complication is usually preceded by a period of prolonged stertor with abundant salivation and respiratory râles, with rapid pulse, restlessness, and signs of general distress.

In the cardiovascular system, raised blood-pressure with tachycardia and inversion of the T-wave in the electrocardiogram

are the usual findings. Some patients, however, especially those of the pyknic habitus, show a persistent bradycardia, the pulse-rate often falling to 50 per minute or even less. There is always a marked increase in blood-flow through the peripheral vessels, and it is probable that this occurs also in the cerebral circulation and plays an important part in the therapeutic process by increasing the supply of metabolites to the cerebral tissues.

As in anoxia, the most important changes are those in the respiratory activities of the brain-tissues. The net effect of the hypoglycæmia on the metabolism of the brain is one of profound depression followed by stimulation in the awakening and post-treatment stages. During the period of coma, the total cerebral metabolism may be reduced to as little as a quarter of the normal. Insulin exerts its action in two ways ; indirectly, by lowering the blood-sugar and so diminishing the available supply of carbohydrate to the whole central nervous system, and directly, by damping down the respiratory activities of the cerebral cells, and so preventing them from burning up the normal amount of carbohydrate.

The cerebral glucose-oxygen metabolism can be measured quantitatively by obtaining specimens of blood from the internal carotid artery and internal jugular vein and estimating the arterio-venous difference in oxygen and glucose-content under different conditions. This procedure gives a reasonably accurate measure of the amount of oxygen and glucose consumed by the brain-cells during the passage of the blood through the cerebral vascular tree.

It is found that, in the untreated patient, the arteriovenous differences did not differ from those of the normal brain, nor was any alteration in the values noted in the post-treatment period. During coma, however, a definite reduction in the arteriovenous difference was found. Within an hour of the injection, the arterial CO^2 becomes raised, but is restored to the normal value within half-an-hour of intravenous injection of glucose. In patients who develop convulsions, there is a sharp rise in the CO^2 level immediately preceding the fit. This is probably due to depression of the respiratory centre, producing a decreased sensitivity to the normal CO^2 stimulus.

In the normal subject, the difference between the glucose-contents of the venous and arterial blood is about 13 mgms. In experiments on dogs, it is found that the oxygen-consumption of the brain, normally 7.99 volumes per cent., falls to 3.8 volumes

per cent. in intense hypoglycæmia in other words, there is diminished consumption of oxygen and at the same time diminished glucose-utilization. In the human subject, the uptake of oxygen by the brain varies indirectly with the severity of the hypoglycæmic reaction.

Himwich and his collaborators have demonstrated strikingly the differences in oxygen and glucose-consumption between the untreated and the treated encephalopathic, by examining samples of blood from the femoral artery and internal jugular vein before and after hypoglycæmic therapy. It was found that, in the resting patient, the average oxygen and glucose-consumption was 7.04 volumes per cent. of oxygen and 12.5 mgms. of glucose ; after the administration of insulin, these values fell to 6.1 volumes per cent. and 7 mgms. per cent. respectively, although oxygen itself was found to be freely available, since the cerebral venous blood showed a relatively high oxygen-content.

The same workers found that, in the human subject there is little or no alteration in the cerebral glucose-metabolism with an insulin dosage of 40 units or less, but with higher doses a definite decrease in the cerebral metabolism is evident. When deep coma is reached, the oxygen-utilization reaches a very low value. The alkali-reserve of the blood becomes increased, but no change in esterase-activity is noted.

With regard to the possible mechanism of insulin-action, it has been demonstrated by Hoffmann that the same physiological mechanism is involved in both the anoxic and hypoglycæmic reactions. Hypoglycæmia acts on the nervous system in a similar manner to oxygen-deficiency, the rate of oxidation being reduced in both, while the sensitivity of the nervous system to anoxæmia is greatly increased by hypoglycæmia, and vice-versa. In this way the combination of anoxæmia and hypoglycæmia produced by insulin therapy produces a much more effective sympathetic stimulation than would be obtainable by means of either alone. It would appear from these considerations therefore that the mechanism of clinical improvement is a combination of reduction of the oxidation-rate of the nervous system with sympathetic stimulation.

It has been shown by Tietz that during insulin-coma there is a rise in the adrenaline-content of the blood. This and the sympathetic activity produced tend to antagonize the insulin-action, since it has been shown by McDonough that in the sympathectomized dog the sensitivity to insulin is much greater than in the

intact animal. It would appear from these observations that in the recovered patient, as compared with those who are clinically unimproved. there is an increased and constant level of adrenocortical substances in the blood. It has been suggested on these grounds that in metabolic encephalopathy there is a defect in the functions of the adreno-sympathetic mechanism, which is corrected as the result of neurometabolic therapy in recovered cases ; in clinically unimproved patients, on the other hand, the failure to improve may be due to irreversible changes or to a constitutional inadequacy of the autonomic system.

(5) The Neurological Phenomena of Hypoglycæmia

In a recent paper on the neurological signs found in hypoglycæmia, Himwich has pointed out that the signs observed follow a definite and regular order. The most highly-developed parts of the brain, which are the most sensitive to the anoxic-hypoglycæmic disturbance, are affected first, followed by the more primitive and less-developed centres in descending order of development ; the sequence of events thus obeys the law of phylogenetic dissolution originally described by Hughlings Jackson.

Himwich describes a sequence of five stages or symptom-groups, corresponding to the depression of the higher centres in the cerebral hemispheres and cerebellum, and the release in turn of the subcortico-diencephalic, midbrain, upper medullary and lower medullary levels in this order.

The first stage, that of depression of the higher cerebral levels, sets in about half-an-hour following the injection. Its onset is indicated by muscular relaxation, tremors, hypotonia, somnolence, clouding of consciousness, and excitement, which last symptom may become extreme towards the end of this phase. It is accompanied by the signs of parasympathetic excitation, but if the patient is disturbed, these may be replaced by the signs of sympathetic overaction.

The second stage, release of the subcortico-diencephalic centres, is indicated by characteristic motor and sensory phenomena. On the motor side, primitive movements with forced grasping, myoclonic twitchings, clonic spasms and restlessness due to release of the subcortical motor nuclei appear, and these may go on to a typical insulin-convulsion. On the sensory side, there is increased sensitivity to stimuli, sensation becomes less discriminative but more intense, and the power of localizing

stimuli is lost. The response to stimulation is of the painful protopathic type, and a strong stimulus produces an abnormally large and intense reaction both in the brain-waves and muscular contractions ; thus, for example, stimulating the sole of the foot results in a total leg-response. At this stage the signs of sympathetic release become evident in the form of exophthalmos, tachycardia, and cutaneous pallor. Convulsions are most likely to occur on release of the medial thalamic nuclei and hypothalamus, which produces the greatest sympathetic activity.

In the third or mesencephalic phase, characterized by release of the midbrain-nuclei, the sympathetic signs pass off and give way to parasympathetic preponderance. The patient's body assumes the characteristic posture of decerebrate rigidity, the legs being rigidly extended, the feet in plantar flexion, and the arms in a position of flexion and pronation. Independent movements of the eyeballs occur, due to release of the nuclei of the third, fourth, and sixth cranial nerves, and powerful muscular spasms set in. With each spasm, the pulse accelerates, the blood-pressure rises, and the pupils dilate with failure to react to light at each dilatation. The Babinski sign is seen at its best during this stage.

In the fourth or myelencephalic stage, the position is one of extension with marked opisthotonus. The pupils become dilated, and do not react to light. The head is rotated to one side, and extensor-spasms occur on the side to which the head is turned. The pulse is accelerated, owing to the sympathetic once more coming into play.

The fifth or myelencephalic stage shows once more parasympathetic preponderance, with shallow respiration, bradycardia, pallor, contracted pupils with failure to react to light, hypopyrexia, thin watery sweat, muscular relaxation and loss of the corneal reflexes. This stage marks the danger-point of the coma, and is an indication for immediate intravenous termination.

Recovery after glucose-administration takes place in the reverse order to that described above, the lower levels recovering first, and finally the higher cortical levels. As in electroanoxia, amnesia is usually complete. Himwich considers that the best clinical results are obtained when the fourth phase is allowed to persist for an hour or more, and that rousing the patient during the hyperkinetic phase usually gives considerably inferior results.

(6) The Psychological Changes in Neurometabolic Therapy; Theories and possible mechanisms of its action

The correlation of the mental changes observed during anoxic and hyperglycæmic therapy with the biochemical effects is less easy than their actual description. A brief revue of the present-day theories of their mechanism will therefore be first presented, followed by the writer's observations drawn from his own case-material.

The theories of its mode of action are of two kinds—the psychogenic, which hold that neurometabolic therapy is non-specific and its effects purely psychological, and the physiogenic, which postulate a direct specific action on the cerebral metabolism.

The earliest of the psychogenic theories advanced was that the therapeutic effect was primarily due to the acute fear-reaction produced by the aura (in cardiazol therapy), sudden break of consciousness, feelings of impending dissolution, and other death-like experiences. This theory has now been abandoned, since fear of the treatment is not necessarily always associated with a favourable clinical result; in the writer's experience, this attitude of the patient has rather been found to militate seriously against the success of the treatment. Moreover, electroanoxia, in which there is instantaneous unconsciousness and absence of aura, is equally as effective in the treatment of dysoxia as is cardiazol-anoxia. The presence of persistent apathy and indifference on the part of the patient throughout the course of treatment is certainly not a favourable sign, but rather an indication of irreversible damage to the thalamic nuclei and corticothalamic connections.

Other theories, such as that of Schilder, suppose that the sudden unconsciousness is identified in the patient's mind with death, and the awakening is the rebirth of the psyche; the transitory period of euphoria which often follows the treatment is interpreted as the joy of rebirth, by which process the patient's previous libido-fixations lose their power, so that his normal interest and affection for those nearest him becomes reactivated. Hemphill suggests that the period of helplessness and dependence immediately following the fit produces a breaking-up of the encephalopathic withdrawal from society, the fit thus helping to reintegrate the personality.

The psychoanalytic view, first put forward by Flescher, rejects the fear-motive for the reason that subconvulsive doses

produce poor results despite the loss of consciousness, while suicidal dysoxics rapidly lose their suicidal tendencies after a few treatments, since it is unlikely that the death-threat alone would effect improvement in patients with suicidal tendencies. His interpretation is based on Freud's theory that melancholia following the loss of a beloved person depends on a strong ambivalent attitude towards the love-object, which is identified with the ego, and aggressiveness which is primarily unconscious is directed against it in the form of guilt-feelings and the self-destructive tendency. According to this theory, the fit by means of its motor phenomena discharges the energy of the destructive and death-drives ; as life is regarded as a contest between Eros, the love-instincts, and Thanatos, the death-instincts, the discharging-function of the convulsion is a support for Eros.

Gluck believes that the important factor is the amnesia, which has a selective effect on the mental functions ; this property of the electroanoxic fit will be further referred to later in this chapter. However, as it seems probable that other factors besides the loss of consciousness are important in the mechanism of cure, this theory alone does not seem to be an adequate explanation ; since it fails to explain the ineffectiveness of barbiturate-narcosis or general anæsthesia, which also produce amnesia and unconsciousness, in ameliorating the symptoms.

Cheney and others hold that neurometabolic therapy is merely an adjunct to psychotherapy, and not a specific remedy. This theory quite fails to explain its efficacy in cases which, if treated by conservative methods would deteriorate steadily, and the fact that the treatment is effective whether or not psychotherapeutic measures are employed in conjunction.

The physiogenic theories are concerned principally with anoxæmia and autonomic changes. Meduna now considers that in electroanoxia the most important therapeutic factor is a direct stimulation of the medulla, producing a beneficial effect on the respiratory centres and autonomic system, his original theory of biological antagonism between the metabolic and convulsive disorders having been found to be untenable. Other theories are an alteration of cerebral water-balance (Wilmans), irritation of the cell-membrane stimulating cell-permeability (Georgi) ; improvement of general physiological functioning rather than direct stimulation of the brain (Squires and Tillim) ; specific stimulation of the midbrain vegetative centres (Pfister and Ewald). Gellhorn, as the result of his work on conditioned

reflexes and autonomic changes, holds the view that neurometabolic therapy acts by virtue of a specific stimulation of the sympathetic system, believing that a general deficiency of sympathetic function is the underlying fault in metabolic encephalopathy. Angyal advances the theory that the beneficial effect is due to stimulation of diseased neurones by hyperæmia following ischæmia, which may act by flushing the brain of toxic metabolites.

Some workers, such as Bowman and Muller, believe that the treatment acts by destroying and eliminating diseased nerve-cells, and so permitting the remaining healthy cells to take over their functions—that is to say, improvement is effected at the expense of producing a destructive lesion, after the same fashion as in leucotomy. This theory is in the writer's opinion quite untenable, since, in order to influence the symptoms to any extent, it would be necessary to destroy such a large amount of brain-tissue that the "recovered" patient would almost certainly show a considerable degree of permanent mental impairment. In point of fact, in successful cases the opposite of this state of affairs is found, and there is complete restoration of normal cerebral function, whereas it is in the partially recovered and unimproved cases that the signs of neuronic destruction at the highest level are found.

Others, like Freeman and Shapiro, support the theory of organic brain-damage, but believe this to be only temporary and effecting a break in intrapsychic tension, thus leading to a more rational mental attitude of the patient. Ziskind emphasizes in this connection the importance of the temporary post-convulsive amnesia, which he considers to be a loss of normal function, and its recovery a loss of abnormal function.

Himwich and Fazekas, who have done most of the work on cerebral metabolism and its pathology in America, emphasize the importance of the metabolic depression produced and the process of phyletic dissolution already described. They hold that the temporary blacking-out of the higher centres and replacement of their functions by the more primitive lower layers is the important factor in recovery.

It will be apparent from a consideration of the facts outlined above that none of these theories gives an entirely satisfactory explanation of the beneficial effects of neurometabolic therapy. A brief description of the psychological changes observed in the course of the treatment will now be given, and some general

deductions presented from a consideration of the known facts.

In the first place, both the anoxic and hypoglycæmic treatments have the property of producing a profound disturbance of consciousness. In the case of electroanoxia, this takes the form of a sudden and complete blacking-out at the moment of application of the current, while in hypoglycæmia there is a profound narcosis of gradual onset. This disturbance of consciousness appears undoubtedly to be one of the essential therapeutic factors; it does not occur in the histamine-insulin method of treatment, and in consequence this method is greatly inferior to the anoxic and hypoglycæmic therapies, in spite of the high degree of autonomic stimulation attained thereby.

As the result of the disturbance of consciousness, a marked degree of temporary amnesia is produced, especially with electroanoxia. Patients state that the painful memories and experiences from which they suffer are dulled and finally blotted out as a result; the intellectual disturbance, on the other hand, is temporary and of mild degree only. The process of first repression and finally true forgetting of the painful and torturing encephalopathic experiences is thus directly aided and facilitated by the breaking of consciousness. The rhythm of the encephalopathy is in this way broken up, while the rhythm of normal mental life and consciousness is restored. The amnesia is usually profound, and very often complete in recovered cases. Acute dysoxics and dysglycics who have remitted completely have in nearly all cases a massive amnesia for their acute hallucinatory and delusional experiences, which may easily be mistaken for lack of insight. At the same time, there is amnesia for the actual events which occurred during the period of the illness, but not for those immediately preceding and precipitating the breakdown. It will be apparent that this is the opposite of what occurs in narcoanalysis in cases of hysterical fugue and amnesia. This amnesia in the writer's opinion is a definitely desirable result of treatment, since unpleasant and irritating memories are abolished thereby; on the other hand, as it does not affect the intellectual functions or memory for the events preceding the breakdown, the amnesia does not in any way militate against the use of subsequent psychotherapeutic measures. These facts would therefore appear to support Gluck's view that the amnesia is one of the essential therapeutic mechanisms.

In those cases where confusional symptoms during the illness were absent and in whom amnesia does not occur, the treatment

seems to have the effect of taking the sting out of the patient's experiences, and enabling him to reorientate his mental attitude towards them.

With the progress of the treatment, there is a gradual and progressive improvement in the habits and co-operation of the patient. Excited and violent dysglycics become calmer, more co-operative, clean in habits, and less liable to impulsive outbursts, while stuporose and inaccessible dysoxics become accessible and lose their mutism and negativism. Rapport and insight in both types improve rapidly, thus facilitating the use of ancillary measures such as occupation and psychotherapy. At the same time, hallucinations and delusions become progressively less vivid and distressing, and the patient's preoccupation with these and other aspects of his phantasy-life becomes much less marked ; normal interests in the outside world return, indifference and incongruity of affect gradually disappear, and the normal range of emotional response is restored. Insight into the encephalopathic symptoms first makes its appearance at this stage, and the power of distinguishing between the real and unreal begins to reappear. The psychological changes produced as the result of neurometabolic therapy are thus similar to those following leucotomy, namely, release of tension, increased extroversion, and complete reorientation of the patient in his relationships to himself and the outside world.

The mental changes are undoubtedly due partly to the direct effect of the treatment on the cerebral metabolism, and partly to the general stimulation and toning-up of the autonomic system. The metabolic changes are seen in the improvement in the general health, return of appetite, gain in weight, and rapid abolition of toxæmia. Most patients state that they feel a definite sense of well-being following the treatments, which is described subjectively as a feeling of being brighter, more lively, and more like their natural selves. They often say that after treatment they are able to think and concentrate more easily. It would seem that neurometabolic therapy, in addition to the specific metabolic effects produced, has a general tonic or stimulating action ; since some patients suffering from depressive neurotic states, in whom the signs of metabolic encephalopathy are absent, frequently describe this eutonia and increase in general fitness following anoxic therapy, even though the underlying neurotic disturbance is unaffected.

Both forms of therapy seem to have a specific effect in dis-

charging or releasing psychic tension, and restoring normal feeling-tone. In the case of depressed dysoxics, whether of the dull, retarded or the tense, agitated type, anoxia appears to have a specific euphorigenic effect, which is not produced by drugs which normally induce euphoria in the normal or neurotic individual, such as benzedrine, alcohol, or euphoriant alkaloids. This appears to confirm that disturbance of cerebral oxygen-metabolism is the cause of the dysphoria in dysoxia, since it is now generally agreed that nearly all the known euphoriant drugs themselves act by virtue of their depressant effect on the oxidation-mechanisms of the brain-cells, while dysoxic depression is not improved by the exhibition of hypoglycæmia. This last fact seems to confirm that in dysoxia the oxidation rather than the glycolyzing functions of the brain are the mechanisms at fault.

In dysglycia, insulin has a definite antagonizing effect upon the excitement, elation, overactivity, and affective disorder, while anoxia is quite without effect on these symptoms. This would indicate that the characteristic emotional and affective phenomena in this condition are due primarily to a disturbance of the glycolyzing mechanisms and not of the oxidation-processes of the cortical and thalamic cells.

In connection with the general cerebral response to neuro-metabolic therapy, mention should be made of the recent work of Gellhorn in America on the effects of experimental cardiazol-convulsions on the conditioned reflexes of animals. He found that in the cat the action of cardiazol on those systems which are innervated by the autonomic nerve-complex produced in addition to the convulsion certain other effects, even when the animals were curarized. These effects included a fall of blood-pressure, dilatation of the pupils, contraction of the nictitating-membrane, and increased sweating—in other words, the typical autonomic syndrome seen in the human subject. The net effect was that the sympathetic reflexes could be more readily elicited for a period of several hours following the fit than in the normal resting state. Thus, the effect of the experimental convulsion is a general increase in excitability of the sympathetic centres. Further experiments on rats showed that in conditioned animals those conditioned reflexes which had been allowed to become lost by desuetude were restored after application of anoxic and hypo-glycæmic therapy. It was found that, of the three forms of neurometabolic therapy, the order of potency in restoring the

reflexes was insulin, cardiazol, electroanoxia. In shock-resistant animals, it was found that the exhibition of thyroxin greatly enhanced the conditioned reflexing-power of neurometabolic therapy. It was thus concluded that the action of the thyroid was central, as the dosage employed did not produce an increase of the peripheral sympathetic effects of the drug.

It seems very probable that this mechanism operates also in the encephalopathic patient treated with anoxic and hypoglycæmic therapy, and is in part responsible for the general feeling of well-being, improved affective response and receptivity to normal ideas and impressions, and increase of rapport already described.

(7) Effect on Individual Syndromes

In dysoxia, the most striking and dramatic change observed in electroanoxia-treated cases is rapid abolition of mental confusion, stupor, and depression. The memory-defect also shows a rapid response to anoxia, the patient stating usually that he feels clearer and able to think more easily. Apathetic, listless patients of the simple dysoxic type say that they feel " more lively," have more energy, and feel a return of normal interest and activity as a result of the treatments. Anoxia seems to be as specific for apathy and indifference as it is for dysoxic dysphoric states.

In the agitated forms, release of tension is shown by the rapid abolition of insomnia and nocturnal restlessness ; in the paranoid types with nociphronic hallucinosis and emotional reaction of acute fear and apprehension, the treatment has a very definite calming effect. To judge from the comments of the patients themselves after electroanoxia, it seems that the break of consciousness and transient memory-impairment with clouding of consciousness induced by the convulsion have a sort of numbing or narcotic effect on the unpleasant memories and affective material. " It makes you forget," and " I don't think so much about things since the treatment " are typical of the kind of comments made by anoxia-treated patients who are in process of recovery. It would seem that the temporary memory-disturbance is a definitely beneficial psychological result of the treatment, contrary to what has been suggested by some of the opponents of neurometabolic therapy, since it is always transient and no permanent intellectual damage is produced thereby.

Dysoxic hallucinosis responds in the same way, the delusions and sensory phenomena "fading out" gradually with each treatment, and showing improvement *pari passu* with the primary affective disturbance. This is particularly well seen in the affective and malignant types. In the paranoid form, especially the agitated type, the hallucinosis is of a much more vivid and disagreeable type, and as a rule is more difficult to influence with anoxia (see Cases 7 and 8). It appears that the fleeting and intracampine type of hallucinosis found in malignant dysoxia is much more susceptible to electroanoxia than that of the paranoid form, in which the most complete examples of projection and dissociation are encountered.

In dysglycia, the most striking effect of hypoglycæmia is its action on the acceleration of thought and associational disorder. In the same way as anoxia is specific for the retardation and depression of dysoxia, hypoglycæmia has a specific slowing-down and tranquillizing effect on the pathological acceleration and ataxia of the thought-processes which is the essential feature of the dysglycic lesion. This dramatic response is seen at its best in the simple manic and acute malignant forms. The excitement, impulsive tendencies, habit-disorders, and destructiveness, which are secondary symptoms, improve *pari passu* with the primary symptoms.

Dysglycic hallucinosis of the malignant type is, generally speaking, highly susceptible to hypoglycæmia, and the same is true of the delusional features. In the paranoid type, the hallucinations and delusions are more fixed and systematized, and so more resistant to treatment, particularly as this form of dysglycia is usually of much longer duration than the simple and malignant forms.

The restlessness, noisy outbursts, overactivity, and dirty habits are usually the first symptoms to show a response to hypoglycæmia, and the most violent, impulsive, and unpleasant types of patient often become comparatively tranquil and co-operative after the first half-dozen or so injections. Next in order of improvement come the sensory features, and finally the delusions and associational disorder. Insight is usually the last sign of improvement to appear. In the fulminating types, disappearance of toxæmia and increase in weight, with return of appetite, are early and rapid.

(8) General Conclusions

In the writer's opinion, no one alone of the theories outlined above offers an adequate explanation of the mechanism of cure in anoxic and hypoglycæmic therapy. The autonomic theory is disproved by the fact that stimulation of the sympathetic-parasympathetic complex alone is therapeutically ineffective, as exemplified by the results of benzedrine administration (sympathetic stimulation), and histamine-insulin therapy (parasympathetic stimulation). A temporary break of consciousness appears to be an essential mechanism, although this alone is insufficient to effect improvement, as shown by the ineffectiveness of narcosis and the fact that mental improvement in hypoglycæmia is often evident in dysglycics long before coma, or even somnolence, is attained. Cerebral anoxæmia alone is in the same way ineffective in dysoxia, as shown by the poor results obtained with nitrogen-inhalation as compared with the convulsive methods. The common factor in both forms of therapy seems to be the specific action of anoxia and hypoglycæmia on the respiratory mechanisms of the cerebral tissues, the action being one of powerful depression of the oxidizing and glycolyzing reactions, followed by a compensatory post-treatment stimulation. The psychological concomitants of neurometabolic therapy would appear to play a relatively minor part in the process of recovery. The autonomic phenomena, in conjunction with the other effects, are undoubtedly an important, if not essential, part of the therapeutic mechanism.

To sum up, it would seem that in the process of recovery three closely interconnected and synergistic mechanisms are involved; depression followed by stimulation of the oxidizing and glycolytic respiratory processes of the brain-cells, temporary breaking of consciousness, and stimulation of the entire autonomic system. To these may be added a third and more indefinite factor, namely the general non-specific tonic effect of the anoxic and hypoglycæmic forms of therapy.

CHAPTER XIV

PSYCHOSURGERY IN THE TREATMENT OF METABOLIC ENCEPHALOPATHY

The operation of prefrontal leucotomy, or lobotomy, is, next to the neurometabolic therapies, the most striking advance in psychiatric therapy during the last ten years. The writer himself has had no personal experience of this form of treatment, since the types of patient met with in military practice are by their nature unsuitable for neurosurgical procedures. Nevertheless, the results obtained so far in civilian cases have been so impressive in certain types of patient that a work of this kind would be incomplete without a reference to the technique and results of the operation. This chapter will therefore present a brief summary of the general position and trend of opinion regarding leucotomy and its applications among psychiatrists in this country at the present day.

The procedure was originally suggested and practised by Moniz of Portugal in 1936, and first tried out in this country on encephalopathic patients in 1940. The theoretical basis of the operation is that the frontal lobes are the seat of some of the highest-developed personality-functions of the brain, and the observation that injury to this region (whether accidental or surgically produced) results in a marked personality-change with little or no evidence of damage to the higher intellectual functions. The alteration in personality is in the direction of elevation of mood, loss of inhibition and self-awareness, and increased extroversion.

The operation itself consists of severance of the association-fibres in the white matter of the frontal lobes, which connect the frontal cortex with the thalamic centres. The tracts divided are the cortico-striate connecting the frontal cortex with the dorsomedial thalamic nuclei, the prefronto-pontine which runs from the cortex to the substantia nigra and dorsomedial pontine nuclei, the cortico-mesencephalic running from the prefrontal region to the medial tip of the cerebral peduncle, and the cortico-striate fibres which pass from the frontal area to the globus pallidus. It is known that frontal lobe lesions in man produce a defect in

association and inability to synthesize problems and situations presented by the external environment, and it appears likely that the dorso-medial thalamic nucleus plays the part of an integrating centre for all somatic and visceral sensory impulses.

The actual operative procedure consists in introducing a leucotome, an instrument which might be described as a kind of refined egg-whisk, into the white matter of the frontal lobe immediately anterior to the tip of the anterior horn of the lateral ventricle, and rotating it so that the cutting component cuts a core of white fibres, thus severing the connections listed above. The site of election for the insertion of the leucotome is taken as the point 3 cms. posterior to the lateral bony margin of the orbit and 5 to 6 cms. above the zygoma. The insertion is made through two burr-holes trephined in the skull, and is thus a blind operation. Anatomically, the object is to divide the white fibres immediately in front of the lateral ventricular horn without entering the venticular cavity itself. Originally, the injection of alcohol into the white matter was tried as an alternative to the leucotome-method, but has now been superseded by the latter technique.

The type of case generally considered suitable for the operation is the chronic encephalopathic in whom the disease is in the quiescent stage, and therefore unlikely to improve as the result of neurometabolic therapy, and in whom the principal symptom is persistent painful rumination and preoccupation with personal topics. The following clinical types have up to now been considered to be the cases *par excellence* in which the operation is indicated :—

(1) The chronic obsessional states, characterized by persistent painful rumination, anxiety, and intrapsychic tension, which keep the patient so constantly in a state of indecision and preoccupation with his internal conflicts as to exert a paralysing effect on all normal activity and enjoyment of life. Those with marked ideas of guilt, obsessional fears, inability to make decisions, and morbidly-exaggerated feelings of self-consciousness fall within this group. It is well known that obsessional conditions of this type are among the most disabling of all mental disorders, and at the same time the most intractable to ordinary therapeutic measures. As pointed out in a previous chapter, there is good reason for classifying some at any rate of these conditions among the true dysoxic states.

(2) The typical encephalopathies, in which the patient's main symptom is constant preoccupation with unpleasant hallucinations and delusions, and the personality and emotional response are still relatively well-preserved and the disease is chronic and stationary. Examples of this type are chronic paranoid dysoxia and dysglycia, and the simple affective dysoxias which have not responded to electroanoxia.

(3) The chronically excited, noisy, impulsive, and destructive type, whose behaviour is largely influenced by their delusions and hallucinations and who may be rendered more tractable and co-operative to nursing as a result of the operation and the subsequent release of tension. Examples of this type are chronic deteriorated dysglycics of the malignant form, and chronic paranoid dysglycics.

(4) Cases of chronic depressive dysoxia, which have either made a poor response to anoxia, or have remitted but tended to relapse repeatedly, and in whom the depression is associated with persistent rumination and preoccupation with ideas of guilt and unworthiness. The involutional form is a good example of this type of case.

(5) Sexual psychopathy, especially chronic homosexuals with marked anxiety, obsessive fears, and ideas of guilt.

Unsuitable cases include the organic encephalopathies, chronic mania, epileptic states, and very apathetic, emotionally deteriorated encephalopathics whose personality has been so damaged that any substantial restoration of normal function would not be expected as a result of the operation. In the last-mentioned type of case, improvement as the result of leucotomy could not be expected, because there would be no emotional capacity remaining to be utilized, once the influence of hallucinations and delusional ideas had been removed. Chronic simple dysoxia and chronic malignant dysglycia would be examples of this type.

It will be evident from a consideration of this list that leucotomy is a purely symptomatic measure designed to alleviate a specific group of symptoms rather than a cure for any one specific disease or group of diseases ; also, unlike neurometabolic therapy, its principal application is in the treatment of the chronic and stationary, and not the early and active, phase of the disorders under consideration.

The indications for leucotomy may therefore be briefly summarized as failure to respond to neurometabolic therapy, or

a good response to such treatment with persistent failure to maintain remission in a patient whose personality is well-preserved.

The effect of the operation on symptoms is that it takes the sting out of them, although not necessarily abolishing them altogether. Thus, the obsessional patient is relieved of the continual feelings of tension and distress, and is able to view his obsessional ideas with detachment and equanimity, while the chronic encephalopathic is no longer constantly tormented by accusatory hallucinations and autochthonous ideas. The morbid ideas, although still present, no longer possess their peculiar affective significance for the patient, and he is able to turn his conative energies to the normal interests of the outside world. The sensory and ideational symptoms, thus robbed of their sting, gradually tend to become less prominent and recede from the centre of consciousness, and in time may fade away altogether. The patient's mental activities are thus reoriented in the direction of extroversion, so that his conscious life no longer revolves constantly round a fixed constellation of ideas.

The immediate complications of the operation include accidental severance of one of the branches of the anterior cerebral artery by the leucotome, with resulting death from cerebral hæmorrhage, and this is the principal operative risk involved. Urinary incontinence, excessive drowsiness and mental confusion due to reactionary cerebral œdema, retention of urine, and post-operative pyrexia are the less serious and temporary complications. Remote complications include unequal pupils and hemiplegia as a result of dividing the fibres too far posteriorly, late development of epileptic fits, and dementia with fatuousness, excessive euphoria, and lack of self-control ; this last sequela is also the result of section too far back.

The principal causes of failure to improve mentally after leucotomy are excessive personality-deterioration—due in most cases to a varying degree of diffuse atrophy of the frontal lobes—and section insufficiently far back, interrupting only a small proportion of the white fibres ; in these cases, a subsequent operation later may be required. Section too far posteriorly may lead to serious personality and intellectual impairment of the type already described.

Mental improvement following the operation may be sudden and dramatic, as in the obsessional cases, or prolonged and gradual, as in the chronic hallucinatory patients, continuing for a period of a year or more following the operation. The leucotomized

patient is in a very suggestible and psychologically malleable condition, which has been described by some authors as a " surgically induced childhood." Rehabilitation in the form of careful training and psychotherapy is of the greatest importance at this stage ; some advocate a prolonged stay in hospital after operation for this purpose, while others advise discharge within a few weeks of operation, in order that the patient may resume his old interests and accustom himself to extramural life as soon as possible.

Freeman (1942) has summarized the personality-changes found in the leucotomized patient as follows. There is freedom from anxiety, worry, and feelings of inferiority, and the patient loses interest in himself both as to his body and his relationships to the outside world. There is increased extroversion with abolition of obsessional thinking, and emotional changes are seen in an increased vividness of the response to external impressions, loss of emotional inhibition, and shallowness with speedy evaporation of the emotional response. There is a general mood-change in the direction of euphoria, and a certain tendency to childishness of manner. Anatomically, it might be said that patients of the type suitable for leucotomy suffer from excessive activity of the frontal lobes ; when the connections of these with the centres for affective and sensory impressions have been cut, the frontal lobes no longer are able to exert their function of excessive inhibition, which sets up the symptoms of excessive self-awareness and affective tension.

In the intellectual sphere, a certain degree of rigidity in categorical attitude is apparent, with inability to find new methods of solution for difficult problems and inability to retain in consciousness simultaneously a number of concepts simultaneously presented. There is disturbance of temporal patterning of activity, and lack of ability to synthesize and to arrive at a correct solution to a situation after consideration of all the factors involved, with inability to see the results of planned acts as they relate to the patient himself. The leucotomized patient thus tends to live for the present and takes no thought for the morrow. These changes usually tend to disappear gradually during the first few months of the post-operative period.

On the whole, the remarkable fact is that there is so little disturbance of the higher cerebral functions, considering the destructive nature of the operation. It certainly seems true, as Golla has pointed out, that the different functions of the nervous system are not rigidly localized, and that when one portion is

damaged irretrievably, its functions can be taken over and performed satisfactorily, if not better than before, by the other parts. The high degree of development and complexity of the frontal lobes would suggest that they are indispensable in man, yet this does not appear to be the case, and in the leucotomized subject it would appear that its functions are mediated through less direct and more roundabout conduction-paths. It is probable that after leucotomy the functions of the direct fronto-thalamic tracts are taken over by the tangential association-fibres lying in and immediately beneath the cerebral cortex, since these are unaffected as a result of the operation.

The importance of leucotomy would appear to be in its application as a new and more hopeful method of approach to the therapy of chronic encephalopathics and the obsessive-ruminative states. If it does not produce a " cure " in the true sense of the word, it is capable of giving great relief from otherwise incurable mental suffering, and making the patient happier and more contented, so that he is enabled to live a useful life, inside or outside of an institution. In many cases it may enable to leave hospital and lead a reasonably normal life a patient who would otherwise be doomed to linger on in incurable mental misery in a chronic mental hospital ward, a burden both to himself and to the patient and long-suffering ratepayer.

The most successful results so far have been in chronic obsessional cases, an 80 per cent. success-rate having been attained at some clinics. In chronic dysglycia, the results have been far less encouraging; this is perhaps only to be expected, in view of the havoc wrought by this disease on the cortical neurones and association-tracts. It is difficult to see how a favourable result could be expected from a destructive operation on a brain in which a large proportion of the cortical neurones have already been destroyed by the dysglycic process. In chronic depressive dysoxics, the most beneficial effects are exerted on the ideas of guilt and rumination, rather than on the dysphoria itself. Chronic disturbed cases are, generally speaking, rendered far more tractable and less resistive to nursing as result of the operation, while destructive and violent tendencies are also greatly diminished.

As against the beneficial results of leucotomy, we must bear in mind that it is a destructive operation, and carries with it the possibility of producing irreversible and not always desirable changes in the patient's personality, such as have already been

described. Thus, although the leucotomized patient may be much happier and more contented than in his preoperative state, he may become a serious problem to his relatives on account of indolence and lack of consideration for the normal inhibitions imposed by society. In the case of the sexual psychopath especially, the ideas of guilt with their consequent inhibitory effect on the abnormal impulses may be abolished, while the latter abnormalities remain, and may actually be accentuated as a result of the removal of inhibition.

Like the neurometabolic therapies, leucotomy has come in for its full share of virulent abuse and biased criticism from certain of the hotheads of the conservative school, the usual argument being advanced that it constitutes a barbarous and mutilating procedure. The most sensible view is undoubtedly that it is no more barbarous and mutilating that the resection of a few feet of intestine for carcinoma or thyroidectomy for thyrotoxicosis, both massive adventures in surgery which are undertaken readily enough by the surgeon. Leucotomy is closely analogous to such procedures as the operation of spinothalmic-chordotomy for the relief of intractable pain in malignant disease, and its use has been rightly confined up to now to the chronic and otherwise incurable forms of mental disorder.

To summarize the present position, it would seem that the drawbacks of the operation are greatly outweighed by the benefits resulting in a large number of cases, and the operative risks are on the whole slight. Its most outstanding possibility seems to be that it offers a new and much more hopeful approach to the therapy of chronic anxiety and obsessional states, which has hitherto been one of the most baffling of psychiatric problems.

Its main disadvantage is that in its present form it is a blind operation and of necessity a somewhat crude procedure, chance playing a large part in determining the success or otherwise of the operation. A successful result depends largely on making the section at exactly the right place, so as to interrupt a sufficient number of fibres without causing serious damage to the higher cerebral functions. The surface-markings used as a guide for the insertion of the leucotome vary very considerably in different individuals, and for this reason some surgeons have devised a much more elaborate procedure involving a full exposure of the area of operation, so that the tracts are divided under direct vision. The disadvantage of this is, of course, that in place of the

comparatively simple blind leucotome-technique a major cranial operation is involved.

It is likely that in the course of the next few years when the results of the operation have been fully studied and assessed, our knowledge of the frontal connections and their functions will be greatly extended, and with improvements in surgical technique a rational and planned method of approach to the neurosurgery of mental disorders will become a practical possibility.

CHAPTER XV

CONCLUSION

(1)

The pathology, ætiology, and therapy of the metabolic brain-diseases have now been discussed in the light of our present knowledge of cerebral physiology and biochemistry. They may be regarded as organic conditions, with a definite pathology and morbid anatomy, in the same way as such well-known conditions as general paresis, multiple sclerosis, and the degenerative encephalopathies of later life. Their treatment is essentially biochemical and pharmacological, like that of the above-cited disorders, and there is every reason to suppose that it will continue to be so, and that more effective methods of obtaining a permanent cure will be discovered in the near future as further facts are added to our knowledge of the cerebral biochemical mechanisms. It is a striking fact, which not even the most strenuous protagonists of the psychogenic school of thought are able to controvert, that all the great advances in psychiatric therapy made in the last twenty years have been along biochemical and physical lines; thus, the malarial treatment of general paresis, the narcosis therapy of neurotic states, and the neurometabolic treatment of the metabolic encephalopathies have marked a new era in psychiatry, in the same way as the discovery of antisepsis, the sulphonamides, and penicillin have opened up a new era in surgery and general medicine.

There is at the present day an increasing tendency towards the integration of psychiatric theory and method with general medicine, and rightly so. Up to quite recently, psychiatry was generally regarded as an abstruse and recondite branch of medicine, outside the pale of ordinary medical practice and the exclusive province of a few rather eccentric and peculiar individuals. The general attitude of the profession might have been summed up in the words "Ætiology unknown, prognosis hopeless, treatment nil, and leave it at that." It is the author's hope that this work will be of interest to physicians outside the practice of psychiatry, and will help to bring this branch of medicine more

into line with general medical practice, by showing that the conditions discussed in the foregoing chapters are far from being peculiar and mysterious disorders, and can be envisaged in terms of ordinary physical pathology, departing in no manner from the ordinary laws of physical medicine.

Before, however, attempting to apply the facts already discussed to the conditions encountered in civilian psychiatric practice, it will be as well at this point to recapitulate briefly the main differences between those conditions and the forms seen in military practice. There are undoubtedly certain important differences, which raise difficulties in consequence, so that this question will now be more fully set forth and discussed.

(2) Civilian and Military Psychiatry compared

One of the greatest of medical fallacies, perpetuated largely as a result of the experience of the 1914-1918 war, is that the form of encephalopathy found in military practice differs radically from that encountered in civil life. Attempts have been made to show that the wartime " psychosis " is a special type, characterized by an acute onset, a good prognosis, and a strong tendency to spontaneous recovery without special treatment. This idea has recently been revived in one or two articles which have been published in the literature on the subject. It arose originally as the result of faulty observation and diagnosis. It is well-known that there are certain acute psychiatric disorders which arise as the result of acute battle-stress, and are characterized by gross symptoms, such as stupor, panic-reactions, dysphoria, conduct-abnormalities, and a form of pseudo-hallucinosis to which reference has already been made in the chapter on acute neurotic depressions and their diagnosis. Such conditions are common in wartime, and are are almost always labelled " psychoses "—that is, encephalopathy. The author has encountered numerous examples of this type of personality-disorder in the course of his wartime experience. Their prognosis is always ultimately good when removed from front-line conditions, recovery being almost invariably the rule with or without special treatment. Hence the idea arose that " war-psychoses " were a special clinical entity with an invariably good prognosis.

The conditions just mentioned are, of course, not true encephalopathies, but examples of the acute hysterical personality-disorder already described in connection with the differential

diagnosis of encephalopathy and the neurotic depressions. The terms "battle-exhaustion" and "exhaustion-state" have already been referred to in connection with these conditions: an even better term, in the writer's opinion, would be "acute emotional upset (A.E.U.)", since this term would accurately describe their nature and mechanism, while at the same time removing the stigma of "neurotic" from the condition and indicating its non-encephalopathic nature.

Sufficient clinical descriptions and case-histories have been presented in the chapters on Dysoxia and Dysglycia to demonstrate beyond any doubt that the forms of metabolic encephalopathy found in military practice differ in no respect in symptomatology, course, and prognosis from the classical types met with in civilian life. The principal differences are found in the mode of onset, age-incidence, and type of encephalopathy found, and may be briefly summarized as follows:—

(1) In a large proportion of military cases, the onset is much more acute and the clinical symptoms more fulminating than in civil life, the condition being much more frequently a response to severe stress, such as enemy action, climatic conditions, or exposure.

(2) It follows from above that military cases are diagnosed and brought for treatment at a much earlier stage of the disorder than is usually the case in civilian practice, so that the prognosis with neurometabolic therapy is on the whole much more favourable.

(3) The case-material in any series of military encephalopathics is composed almost entirely of physically healthy adults of the age-group 20 to 35 years; hence conditions of chronic physical disease which might militate against successful neurometabolic therapy are rarely encountered, as are the effects of secondary and senile mental deterioration.

(4) It follows from (3) that certain clinical types of encephalopathy are rarely encountered; thus we rarely see true benign dysoxia (manic-depressive states), the chronic delusional dysglycias of later life, and the senile and presenile encephalopathies.

(5) In a military psychiatric hospital, the absence of a large population of chronics results in a much more wholesome and hopeful atmosphere, and the medical officers are able to concentrate on specific therapy, so that the average length of stay in hospital is considerably reduced.

(6) As nearly all patients diagnosed as encephalopathic, whether recovered or not, are eventually invalided from the service, it follows that they are effectively removed from the conditions of stress which precipitated the breakdown. In civilian practice, on the other hand, it often happens that a patient who has broken down as a result of family and domestic difficulties is returned on discharge from hospital to the unsatisfactory milieu which caused the original illness, with the result that relapse occurs within a longer or shorter period.

In civilian practice, in contrast to this, relatively few cases are seen in the earliest stages of their illness, and there is a larger proportion of the more chronic and insidious types, whose early symptoms are so mild that they are usually allowed by their relatives to drift along steadily downhill before being finally brought to the clinic for advice ; by the time that they are seen, irreversible changes have in the great majority of cases set in, and the prognosis is accordingly much less favourable.

A good example of this type of case is the insidious form of dysoxia which commences in late adolescence, and termed in the older text-books " *dementia præcox* " or " simple schizophrenia." A young adolescent or adult, usually of the shut-in personality-type, shows a gradual loss of interest, progressive withdrawal from reality, and deterioration of efficiency ; gross symptoms, such as hallucinosis and delusions, are either absent in the early stages or so fleeting as to pass unnoticed, the relatives never realizing the serious nature of the condition until it is far advanced or a sudden flare-up occurs in the form of an acute hallucinatory-confusional episode. The end-result in such cases is nearly always the same ; the patient goes to swell the chronic mental hospital population.

Another example is the insidiously developing form of sensory dysglycia of later life—the " paraphrenia " or " delusional insanity " of orthodox terminology. In the early stages the ideas of reference and persecution may be vague and transient, and may take the form simply of morbid self-consciousness, being ascribed to " nerves," overwork, or business or domestic worries. In other cases, it may take the form of indefinite hypochondriacal complaints referred to the visceral functions, which are usually treated by the family doctor with a few encouraging words and a bottle of medicine. It is only when the delusional system, that is the irreversible dysglycic change, becomes firmly established, that the patient's relatives begin to suspect that anything is

seriously amiss; the end-result is, of course, the same as in the first type of case cited.

These two hypothetical examples illustrate very well the difficulties encountered when attempting to apply the methods and technique of military psychiatry to the common types of encephalopathy found in civil practice. Any sort of comparison of the therapeutic results is, of course, grossly unfair.

(3) Applications to Civilian Practice

These considerations naturally lead to the important problem of how the lessons and experience of military psychiatry can be applied to the problems and conditions found in civilian practice.

As regards the detection of early cases, the principal difficulty is that we have as yet no reliable biological test for the diagnosis of metabolic brain-disease, as in the case of " organic " conditions. Thus, for early paresis, we have the Kahn and other serological tests, and for early diabetes mellitus, the urinalysis and estimation of the blood-sugar, but in a case of early dysoxia or dysglycia the pathologist can give us no aid, and there is no short cut to diagnosis for the psychiatrist; he must depend entirely on his clinical acumen and on careful and painstaking examination. Metabolic encephalopathy, like some medical conditions, is sometimes the easiest of conditions to diagnose, but as often one of the most difficult. This is especially so when one is confronted with the personality and behaviour-disorders of adolescence and early adult life, particularly as it appears that benign and abortive forms of encephalopathy, possibly of endocrine origin, and with a tendency to spontaneous and permanent remission, occur sometimes in adolescence. The following hypothetical case is fairly typical of this kind of problem.

An adolescent youth or girl is brought to the consulting-room with a history of slight and indefinite personality and behaviour-changes over a period of a few weeks or months. The parents state that he or she has recently shown a tendency to withdrawal from normal companionships, day-dreaming, and inattentiveness, and has perhaps shown a mild degree of falling-off of interest in school-work or been unduly preoccupied with sexual or religious matters. On examination, little or nothing obviously abnormal may be evident, and physical examination is negative. The question then arises of whether the case is simply one of temporary adolescent instability with an ultimately good prognosis, or the

first stage of a malignant dysoxic or dysglycic encephalopathy. Should the anxious parents be simply reassured and the patient referred to the child-guidance or psychotherapeutic clinic, or should they be told that their offspring is in the early stages of a serious form of organic brain-disease, and should forthwith be admitted to hospital for a course of certainly rather drastic and possibly expensive neurometabolic treatment ?

This type of case is one of the most difficult problems in the whole of psychiatry, and indeed, of medicine. To miss the early signs of a malignant encephalopathy in an adolescent or young adult and to fail to institute effective treatment is one of the greatest of medical tragedies. On the other hand, not even the most ardent enthusiast for the new methods of therapy would go so far as to suggest that every adolescent showing signs of temperamental instability should be automatically hospitalized and subjected to a course of anoxic or hypoglycæmic treatment. The latter kind of therapeutic abuse, the result of over-enthusiasm rather than sound clinical judgment, has more than any other factor helped to discredit the neurometabolic therapies in the eyes of psychiatrists of the more cautious and conservative school of thought.

It will be evident from a consideration of these facts that the problem of personality-disorders in adolescence and early adult life and their diagnosis is an extremely important one, as also is careful and painstaking examination in these cases. A ten-minute examination is often more than sufficient in the case of the soldier who has developed a florid encephalopathy under stress of action, but in the type of civilian case just described the examination must of necessity be a much more careful and time-consuming procedure.

(4) How the Problem might be attacked

Every case in which there is any suspicion of early metabolic brain disease should be given a thorough and searching physical examination at the same time as the psychiatric examination, preferably by the psychiatrist himself. No one will doubt the importance of this ; as indicated in the chapter on differential diagnosis from organic conditions the dysoxic syndrome can readily mimic a variety of different diseases. As examples, the author has on various occasions seen cases of epilepsy, general paresis, post-encephalitic parkinsonism, and chronic encephalo-

myelitis sent to him with a diagnosis of metabolic encephalopathy and a request for anoxic therapy.

Special attention should be paid to the endocrine functions, the upper respiratory tract for evidence of chronic sepsis or obstruction, the radiographic examination of the chest, the blood and C.S.F. serology, and, if necessary, the electroencephalogram. The physical type of the patient and the presence or absence of physical stigmata should also be carefully noted.

The psychiatric examination should next be systematically carried out. This would include a detailed history of the family, environmental milieu, previous personality, school and work-record, with details of any past personality-difficulties, and, if necessary, intelligence-tests. The past medical history should be carefully investigated, particular attention being paid to any history of delinquency or previous nervous breakdowns. This last point is of special importance, since it is not uncommon for a patient to give a vague history of a period off work several years previously on account of " nerves," or " nervous trouble," which was treated at home by the family doctor, its true nature having gone unrecognized at the time. Special enquiries should be made as to the existence of any domestic trouble or maladjustment, or of dislike of the patient for his present employment. Especially careful search should be made for any evidence of the shut-in, schizoid type of personality, since the presence of this in association with symptoms of increasing withdrawal from reality and tendency to phantasy is always highly suggestive that the case is one of early dysglycia cerebralis.

Should the physical and psychiatric examinations be inconclusive, various simple therapeutic tests may be employed. In cases where there is evidence of definite maladjustment in the home or in employment, a change of work and surroundings may be advised, and it is here that the services of a trained psychiatric social worker may be of great assistance.

The effect of special drugs, such as bromide or benzedrine, should always be tried in cases where such medication appears to be indicated. For patients who show evidence of conscious or unconscious repression and difficulty in talking freely at interview, the association word-test or narcoanalysis may be employed. In cases where the source of the trouble appears to lie in psychological conflicts rather than in environmental maladjustment, psychotherapy with or without analysis should be used. Endo-

crine therapy should always be tried in patients who show evidence of minor degrees of glandular dysfunction.

Failure to show improvement after a month's trial of the methods outlined above raises the question of whether or not to institute biochemical therapy. In uncomplicated acute cases the indications are straightforward, but more careful consideration is required in the milder types of case commonly encountered in in civilian practice.

Generally speaking, it can be laid down that in early encephalopathy the chances of a complete remission are very much reduced after the manifest symptoms of metabolic brain-disease have been present for a longer period than three months, and the prognosis worsens rapidly after this period. A safe rule to apply in cases of this kind is that more harm is likely to be done by waiting and allowing the symptoms to progress than by instituting early, although perhaps unnecessary neurometabolic therapy.

The following signs may be regarded as the absolute indications for neurometabolic therapy ; persisting or increasing apathy and withdrawal from reality ; persistent causeless depression, which does not respond to drug-therapy or psychotherapeutic procedures ; deterioration of habits or episodes of abnormal conduct ; complaint of bizarre thoughts or ideas, or feelings of reference ; and commencing dyssymbolic changes, as shown by inability of the patient to express his thoughts and feelings in ordinary language. Feelings of depersonalization and unreality are also an indication, since not infrequently these may portend a sudden suicidal attempt. The supervention of this last-mentioned sign or of an episode of mental confusion or excitement are indications for immediate institution of neurometabolic therapy, as also is the appearance of definite hallucinosis, ideas of passivity, or delusional features.

With regard to depressive and unreality-symptoms, it may here be re-emphasized that the commonest cause of endogenous depression for the first time in a patient under the age of 30 years is malignant dysoxia or dysglycia.

The next question is to decide which kind of neurometabolic therapy is to be employed, and whether the patient should be hospitalized or treated in the out-patient department. With regard to this point, some psychiatrists have recently advocated the use of electroanoxia in the out-patient department, and this has been found to be quite successful in the milder cases. There would appear to be no valid objection to this, since the simplicity

of the procedure and absence of complications render it no more of a major operation than, say, the opening of a superficial abscess under nitrous oxide anæsthesia in the casualty-department of a general hospital. Out-patient anoxia would seem to be indicated in the milder forms of dysoxia and derealization-states; in the severer forms with conduct-disorder and suicidal tendencies, hospitalization would, of course, always be indicated, as for dysglycic cases requiring hypoglycæmic treatment.

The relative indications for the two types of neurometabolic therapy have already been discussed, and the same general rules for the distinction of the dysoxic and dysglycic syndromes as set forth in the earlier chapters of this work apply in civilian cases.

The position may be summed up by saying that any personality-disorder of the type described above in an adolescent or young adult, in which no apparent cause or maladjustment is found and which does not respond in a few weeks to ordinary measures, should be regarded as an early metabolic encephalopathy, unless definitely proved otherwise. In the absence of physical or other contra-indications, valuable time should not be lost by temporising and appropriate neurometabolic therapy should be instituted as soon as the diagnosis is reasonably certain.

(5) Some Present-Day Difficulties

The question may well be asked; How can the exhaustive and lengthy examinations described in the foregoing paragraphs be carried out effectively in the average psychiatric out-patient department with the resources available at the present day? It is only too evident that the practical difficulties attendant on the present-day psychiatric health-services are too great to enable the psychiatrist doing out-patient work to devote more than a fraction of his time to adequate examination of this type of case.

It is beyond any dispute that the country's psychiatric services at present are totally inadequate for a properly organized attack on the problem of the metabolic encephalopathies and the equally important one of personality and other psychoneurotic disorders. Adequate psychiatric clinics are few and far between, many of them consisting of an afternoon a week put in by a resident medical officer lent for the purpose by the local county mental hospital. Furthermore, since psychiatry first started as an organized branch of medicine, the total number of attendances at clinics has greatly increased, especially now that education and enlightened propaganda have convinced the average lay person

that no stigma is attached to attendances at the local psychiatric out-patient clinic.

The writer was fortunate in that prior to military service he worked in a progressive and up-to-date hospital, where the medical officers were encouraged to devote a considerable part of their time to work in the out-patient clinic and given every facility for doing so. As a result of the experience gained, the writer was impressed by two things ; the very great amount of time required to make anything like an adequate psychiatric examination, which generally had to be ruthlessly cut down in order to deal with the number of new attendances, and the acute shortage of trained psychiatrists available for the work. A psychiatric examination which is anything like adequate is a much more lengthy and detailed affair than the average examination required for a medical or surgical case, and often requires infinitely more patience and tact, especially when, as often happens, the examiner has to depend for his history on the co-operation of relatives who are anything but intelligent and co-operative. In the author's opinion, a whole day's work would be required to examine adequately the average number of new cases who attend such a clinic at any one session ; at present, this usually has to be telescoped into the space of two or three hours. In addition to this, the psychiatrist usually has to see and hear the complaints of anything up to a dozen or more chronic " regular " attenders at the clinic.

The psychiatric clinic is also more often than not relegated to some cramped and unpretentious corner of the local general hospital, with the result that an overcrowded waiting-room and two or more psychiatrists sharing one small consulting-room and constantly falling over one another is an all too-frequent state of affairs.

The same remarks might be applied to the psychiatric social workers. Like the psychiatric specialists, they are as yet quite inadequate in number to deal with anything like the increasing number of problems in environment, employment, and rehabilitation which the patients present.

As regards mental hospitals themselves, the vast majority are so built and designed as to be quite inadequate and out-of-date as centres for active and progressive modern treatment, while the conditions of chronic overcrowding make extremely difficult the separation of early and recoverable cases from the senile and chronic patients. The medical officer very often finds his insulin-

cases while under treatment have to be relegated to an ill-lit corner of the chronic sick-ward, while the majority of the beds are permanently occupied by senile and bedridden cases.

(6) Future Possibilities and Developments

Before discussing the possible improvements and probable organization of the psychiatric services in the coming national health-scheme, a brief description of the organization of the army psychiatric service during the war-years may be of interest.

During the early period of the war, the army medical authorities came to recognize the importance of psychiatric illness and the psychological aspects of morale, personnel and officer-selection, and general training. As a result, a special psychiatric branch of the medical service was organized, under the direction of a consulting-psychiatrist to the army. To each of the home commands was assigned a Command-Psychiatrist, with the rank of major, and each command was subdivided into areas each of which had its area-psychiatrist, either with the rank of major (Specialist in Psychological Medicine), or captain (Graded Psychiatrist). A similar system was adopted for the various overseas commands.

To the Area-Psychiatrist was assigned the duty of seeing in consultation any cases referred to him by the unit medical officers of the various formations in his area, either by appointment at the clinics held at the principal military hospital in the area, or by actually visiting the units. The disposal of such cases was decided by the Area-Psychiatrist; thus, cases of encephalopathy would be sent for admission to the nearest military hospital specially reserved for such cases, while cases of psychoneurosis would be either admitted to an E.M.S. Neurosis-Centre or to a military unit for neurotic cases. In the case of mental defectives or men suffering from minor personality-disorders due to being in unsuitable employment, the Area-Psychiatrist would advise the commanding-officer of the unit as to appropriate handling and disposal. Another duty of the Area-Psychiatrist was to examine and report when requested on men who were disciplinary problems or awaiting trial by court-martial.

In addition to the Command and Area-Psychiatrists, there were other specialists assigned to special duties; these included psychiatric advisers attached to the Personnel-Selection Department, whole-time specialists attached to military mental hospitals

and general hospitals, and specialist advisers to certain special formations. The author spent the greater part of his military service as a specialist attached to various military hospitals for encephalopathic cases, both from home-service units and from overseas theatres of war.

The duties of the Command-Psychiatrist included supervision of all the psychiatric work in his command, including that of the Area-Psychiatrists and of the psychiatric hospitals. He also saw cases in units, and acted as general adviser in all matters of a psychiatric nature pertaining to the formations in his command.

This system was found on the whole to work very well, and a highly efficient psychiatric service to deal with all aspects, preventive as well as therapeutic, was eventually built up along these lines. In addition, many general duty medical officers from different units attended special courses of instruction in the early diagnosis and prevention of psychiatric disabilities at the principal psychiatric hospitals, as well as in the psychiatric aspects of personnel and officer-selection.

The hospitals were divided into psychotic, psychoneurotic, and head-injury units, and in addition the E.M.S. hospitals provided a certain number of beds specially for the treatment of military psycho-neurosis cases. There were also special units for the training of problem or disciplinary cases, as also for mentally dull and backward men, whose degree of abnormality was considered not sufficient to warrant invaliding on psychiatric grounds.

The principal weakness of the organization was a tendency towards the "watertight compartment" system. Thus, for instance, an Area-Psychiatrist might spend a year or more engaged in purely area and out-patient work completely divorced from clinical hospital work, while a specialist attached to a hospital might spend two or three years continuously in dealing with hospitalized encephalopathics, without ever seeing any area-psychiatry or experiencing for himself the sort of conditions prevailing in military units; this actually happened in the writer's case. Nevertheless, the army psychiatric services were on the whole extremely efficient and well-organized, and the military psychiatric hospitals very well provided with facilities for carrying out the most up-to-date methods of special therapy.

Within recent years, the civilian mental health-services have been improved and reorganized on somewhat similar lines. Thus, each county mental hospital in many districts has an out-patient clinic organized at the local general hospital, usually under the

direction of the Medical Superintendent or his Deputy, who may devote two or three half-days a week to these duties. The cases seen at the clinics include patients referred by their private or panel doctors, problem-children, cases of juvenile delinquency referred for a psychiatric opinion by the local magistrates' courts, and so on. In many more progressive districts, there are special child-guidance and juvenile clinics for the latter types of case. Recently, some general hospitals have adopted the practice of appointing whole-time salaried psychiatrists not attached to the local mental hospital. In addition, nearly all up-to-date mental hospitals employ one or more specially trained psychiatric social workers, whose duties include interviewing the relatives and families of patients, helping and advising discharged patients about employment and domestic problems, and following up their subsequent histories.

The author feels that this system could be extended and improved upon, somewhat on the lines of the army psychiatric services. Thus, whole-time salaried area-psychiatrists could be appointed for the various districts, with a senior director for each group of areas corresponding roughly to the Command Psychiatrist in the army. Their duties would include the treatment of cases in hospital in addition to purely out-patient work, a special ward or department in the general hospital being assigned for this purpose.

(7) Suggested Plan for a Physical Treatment Unit in a Mental Hospital

Reference has already been made to the unsuitability of many mental hospitals built on the old lines as centres for active treatment, and the difficulties attendant on converting them to this use. Neurometabolic therapy in some form now appears to be definitely established as the basis of the treatment of major mental disorders, and it is extremely likely that future developments will be along these lines. The principal difficulty in organizing and running a neurometabolic treatment-unit in the average mental hospital arises from the fact that the male and female sides of the hospital are always built entirely separate, so that either separate units are required, one for the male and one for the female patients, with two medical officers constantly on duty during hypoglycæmic treatment ; if, as sometimes happens, only one doctor is available, he has to divide his time between

the two units, and cannot be at the same time within easy reach of both sides in the event of emergencies.

The layout shown in the attached diagram would appear to the author to be the most suitable, and the suggested plan is the result of several years' intensive experience of these forms of treatment. As will be seen, the unit consists of a single-storey long building divided into three portions by the two partitions in the centre. Of the two lateral portions, one is for the male and one for the female beds; the small central room containing a chair, writing-desk, and examination-couch for the medical officer in charge, also the tables, and cupboards, and sterilizer for the drugs and instruments used. The medical officer's room is separated from the treatment-rooms by glass partitions with curtains or sliding shutters. In this way the medical officer is enabled to keep both male and female wards under continuous observation at the same time, and to hold himself immediately available in the event of an emergency on either side. At the same time, he is able to fill in time by writing up case-notes, reading, or interviewing other patients. At the end of each ward are two small annexes, one for use as an ablution room, and one containing cupboards for storing clothes, bed-linen, glucose and other accessories. The entrances to the male and female treatment-rooms are at each end of the respective wards; in this manner, the whole unit is directly under the medical officer's control, while at the same time complete separation of the male and female sides is effected.

The unit shown in the diagram is designed for eight male and eight female beds, which should suffice for the average-sized hospital carrying out intensive hypoglycæmic therapy. It could be constructed at quite a reasonable cost on the prefabricated system, and has the advantage that it could be employed equally well for other forms of therapy, such as electroanoxia, continuous narcosis, or for use as a general, sick or admission-ward. It could also be used as a unit for research-purposes, such as, for example, a batch of patients undergoing blood-sugar tolerance tests or other biological investigations requiring continuous observation. If required, it could be constructed as an annexe attached to an admission-block or villa instead of as a separate unit, and connected at each end by a covered passage to the male and female sides respectively.

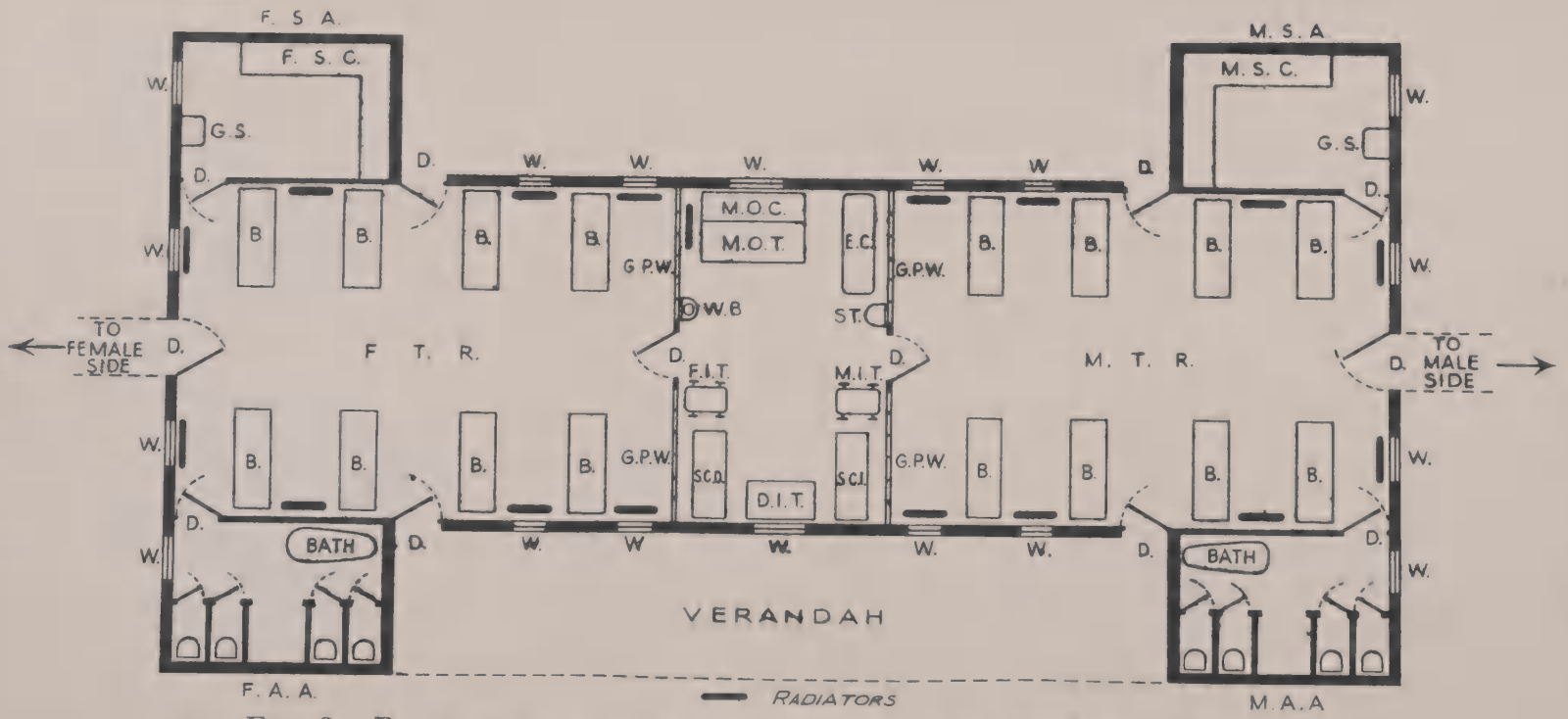

FIG. 3. PLAN FOR LAYOUT OF NEUROMETABOLIC THERAPY UNIT (16 BEDS)

B = Bed
D = Doors
DIT = Drugs and Instruments Table
EC = Examination-couch
FAA = Female Ablution Annexe
FIT = Female side instrument-trolley
FSA = Female stores Annexe
FSC = Female side store-cupboard in Annexe (for linen, etc.)
GPW = Glass partition-walls
L = Lavatories
MOT = Medical Officer's table for writing
MAA = Male Ablution Annexe
MOC = Medical Officer's cupboard (for case-notes, charts, etc.)
MSA = Male side stores Annexe
MSC = Male side stores cupboard
R = Radiators
SCD = Store-cupboard for drugs
SCI = Store-cupboard for instruments
ST = Sterilizer
W = Windows
WB = Washbasin

(8) The Popular Attitude to Mental Disorder ; dealing with Patients' Relatives

One of the most difficult problems in the treatment not only of the metabolic encephalopathies but of mental disorders generally is undoubtedly that of the patient's relatives and their attitude towards mental disorder, reference to which has already been made in connection with the medico-legal aspects of neuro-metabolic therapy.

In recent years, thanks to enlightened propaganda and education, this has been considerably improved. It should always be borne in mind, however, that to the great majority of lay people, educated and otherwise, mental disorder in any member of the family is regarded by the patient's relatives as a major disaster, as also is the idea of his or her admission to a mental hospital.

One of the most striking facts commonly encountered in dealing with patients' relatives is that in many cases they show even less insight into the nature of the illness than the patient himself. They often will simply refuse to accept the idea that he or she is suffering from a mental illness ; to them, the very word " mental " is full of sinister associations, it either being spoken in a spine-chilling whisper ("He's not *mental*, is he, doctor ?"), or in a tone of withering contempt (" But why is he in a *mental* place, doctor ? "). In dealing with this attitude, the tact and wisdom of the doctor may be severely taxed, and reassurance and a sympathetic attitude are of the greatest importance.

" Difficult " relatives can be divided into two main types, the Agitated and Hysterical, and the Know-All type. The former, usually an elderly mother or other female relation, is always liable to become acutely hysterical and to dissolve in a flood of tears when interviewed by the doctor ; this type often has a fixed idea that neurometabolic therapy will have the effect of making the patient " silly " or " weak-minded "—another result of the recent hostile and biased criticism of physical methods of treatment for mental disorders which has lately received so much unfortunate publicity in various journals. It often happens that one of the hardest tasks a medical officer is called upon to perform is that of persuading a relative of this type to sign consent for neurometabolic therapy.

The " Know-All " type of relative is dreadfully familiar to all who have to deal with the treatment of mental disorder. He is usually a querulous, domineering, and self-opinionated type, who has read all the popular pseudo-scientific literature on the subject, and always knows better than the medical officer. He insists on frequent interviews with the doctor, argues in an offensive manner, voices constant criticisms of the hospital, the treatment, the doctors, and everything in general, and is never grateful for anything which is done for the patient. His sole object, in fact, is to place every possible obstacle in the way of the doctor who has to treat the patient, and the tact and patience of the latter is often strained to breaking-point in attempting to deal with this particular brand of psychopathic nuisance, since he is usually about as susceptible to reason and persuasion as an excited dysglycic. It is often found that the surest way of precipitating a relapse in a recovered patient is to send him home on discharge to a household which includes a relative of this type.

In nearly all cases it is found that the relatives' anxiety is centred around four questions, namely ; What are the chances of recovery ? Is the treatment dangerous, or likely to produce deleterious effects physically or mentally ? Will the patient keep well or relapse ? Will he be able to return to work and earn his living or not ?

To the first question the answer, providing the case is one of metabolic disease in the early stages, should be as follows ; provided the proper treatment is given early enough, the patient has every chance of making a good remission, provided that unforeseen complications do not interrupt or compel the cessation of the treatment.

The second query should be answered by a definite assurance that the possible risks and complications of neurometabolic therapy in skilled hands are negligible, the exception being in the case of patients who, in addition to their metabolic breakdown show evidence of co-existing physical disease. To the second part of the question, the answer is, No ; major physical complications in neurometabolic therapy are extremely rare, and there is no evidence that organic cerebral damage ever results from the use of the treatment in encephalopathic patients.

The third question should be answered by saying that, although no absolute guarantee against relapse can be given, the patient's chances of maintaining his remission are as good as those of a healthy individual who has never had an encephalo-

pathic breakdown. The exception is, of course, the patient with a history of previous recurrent episodes, of which the manic-depressive type of dysglycia-dysoxia is the most typical example.

The last question is more difficult to answer, since the ultimate working-capacity of the discharged patient can only be assessed after completion of treatment, and will largely depend on the presence or otherwise of post-encephalopathic residua. A guarded reply should therefore be given by saying that, provided the response to treatment is favourable and a reasonably good remission is obtained, there is no reason why the patient should not ultimately be restored to his previous level of efficiency and working-ability.

In conclusion, it is to be hoped that the conception of a physical basis for the metabolic encephalopathies, as for ordinary medical conditions, may in time serve a useful purpose in dispelling much of the mystery and dread associated in the popular mind with mental disorder ; since, with a little enlightened propaganda, the lay public might be induced to regard mental disease as in no way essentially different from ordinary physical diseases. The adoption of the terminology suggested in this work would also aid in this respect ; since terms like " dysoxia " and " dysglycia," while sufficiently impressive to the ear of the lay public, would be lacking in the sinister significance and associations attached to orthodox terms such as " melancholia " and " schizophrenia."

The problem of after-care of the discharged patient is also one where the co-operation of the relatives is of the greatest importance, and in which the psychiatric social worker is of such invaluable assistance. This is especially the case where the breakdown has been precipitated by unhappy domestic surroundings, and where the return of the patient to his or her previous home-conditions would almost certainly undo the results of weeks or months of successful neurometabolic therapy.

The question of the advantages of voluntary versus certified basis from the relatives' point of view is one which has been dealt with fully by several text-books, so that the writer will confine himself to a few brief remarks only on the subject.

In the writer's experience, the types of case which are absolutely unsuitable for voluntary admission are very hostile and unco-operative paranoid patients, and depressed dysoxics with very defective insight and marked suicidal tendencies. The former are always liable to refuse treatment and insist on giving

notice within a few days of admission, to the distress and anxiety of their relatives, and certification in these cases is nearly always essential if there is to be any hope of carrying out adequate treatment. The latter type of case usually offers a similar problem, and unless a fair degree of insight and ability to co-operate is present, certification is always to be preferred to the risk of suicide occurring after the patient has left hospital against advice. These points should always be strongly urged in such cases where the relatives are strongly opposed to the idea of certification if it can possibly be avoided.

(9) Future Possibilities in Psychiatric Research

Emphasis has already been laid upon the outstanding part played by biochemistry and pharmacology in the therapy of mental diseases, and it is becoming daily more evident that it will be the biochemist and pharmacologist who are likely to provide the answer to the problems of causation and the most important contribution to future therapeutic developments.

Up to now, the search for specific antidotes for the common forms of neurosis and encephalopathy has been largely unsuccessful. As regards the latter group of disorders, no specific drugs are known which are perfect physiological antagonists to the encephalopathic symptomatology, in a similar manner to what is found with certain alkaloid and other poisons. We have, however, an agent of known chemical composition which can reproduce exactly under experimental conditions the encephalopathic syndrome, namely, the mescaline-group of alkaloids, the properties and importance of which have already been discussed. It would appear that here we have the most promising line of approach to the problem, and at this point a further analogy from general medicine may briefly be presented.

It is known that the alkaloids of the curare-group can reproduce almost exactly under experimental conditions the nervous symptoms seen in the neuromuscular disease known as *myasthenia gravis*; in both cases the pathological basis is the same, namely a disturbance of the chemical mechanism at the myoneural junction. It has been found that physostigmine and its derivative, prostigmine, are perfect antidotes both to the experimental paralysis and the natural disease, the chemical mode of action being similar in both cases. The result has been a striking advance in the therapy of a previously serious and often fatal disease.

In a similar manner, it might be by no means impossible to find a substance which was a perfect physiological antagonist to mescaline in the human subject; such an agent would quite possibly exert a similar effect on the symptoms of metabolic encephalopathy, and in a manner analogous to that of physostigmine, be effective in abolishing the symptoms of the encephalopathic syndrome, such as hallucinosis, thought-disorder, and affective disturbances. Such a drug might well be one of the amine or alkaloid-class, or even possibly a derivative of p-phenylenediamine, the substance described by Quastel and others as the specific stimulant of the cerebral respiration-mechanisms. Theoretically, there is no reason why such a substance should not eventually be successfully synthesized, when we consider the enormous advances both in the science of chemotherapy and in the knowledge of cerebral biochemistry which have been made in the course of the last few years.

With regard to the important group of conditions described in this work as the neurotic depressions, therapeutic developments are likely to be on similar lines. The fundamental clinical symptom of dysphoria, or decreased threshold for unpleasant sensation with raised threshold for pleasant affects, indicating a dysfunction of the thalamic and thalamo-cortical systems, has already been described; the logical therapeutic answer to this would be a pharmacological agent which would produce the opposite effect—in other words, a powerful euphorigenic drug, which would have a selective action on the thalamic centres, while at the same time being free from the undesirable side-effects usually associated with drugs of the narcotic group. The successful production of such an agent would enormously simplify the problems of therapy in many of the more chronic and obstinate forms of neurotic dysphoria, and might also have important applications in the treatment of the milder and chronic forms of dysoxic depression.

It is probable that the therapeutic armamentarium of the psychiatrist of the future will consist of a large number of powerful synthetic drugs, possibly of entirely new type, each with a specific cerebral action; thus, he would have available agents with a specific anti-encephalopathic action, and others with a selective action in abolishing dysphoria, obsessional thinking, pathological anxiety, and so on. This is, of course, to a large degree speculation at the present time, but it is the psychiatry of the future and not that of the present with which we are now concerned.

With properly-organized research along these lines undertaken by the organic chemist, pharamacologist, and psychiatrist-biochemist working in close collaboration, these developments, at present mere theoretical possibilities, might well become realities in the course of the next few years and completely revolutionize the treatment of the two most important groups of psychiatric disorders.

(9) Concluding Remarks

Sufficient has been said in the foregoing paragraphs to emphasize the importance and far-reaching medical and social significance of the problem of the metabolic brain-diseases. We have now well-organized health-services equipped to deal with such scourges as tuberculosis, venereal disease, and cancer, but much still remains to be accomplished in the prevention and early treatment of the metabolic encephalopathies.

This group of diseases is one of the most tragic and disastrous conditions, both in its medical and social consequences. It attacks young people, at the most promising age of life ; instead of killing, it transforms them from healthy and active human beings with all the promise of life before them into useless and deteriorated dements, doomed either to linger on for years in the chronic wards of a mental hospital, or to become a permanent burden on their families and relations. The cost of maintaining these thousands of useless lives is a burden on the already sorely-tried taxpayer, and it is high time that this disease was listed, like the conditions already mentioned, as a public enemy, and the public brought to realize its seriousness and social consequences.

Metabolic encephalopathy is a curable and even preventable condition—provided diagnosis be early and treatment thorough and adequate—and this last statement cannot be repeated too often. The writer would even venture to say that, provided these two conditions are fulfilled, a 90 per cent. cure-rate in early cases might well become a possibility, and that most pathetic of medical tragedies, the post-encephalopathic dement of the chronic mental hospital ward, might one day become nothing more than a pathological rarity. Even in those types of encephalopathy which relapse, adequate neurometabolic therapy offers the hope of preventing deterioration, of keeping the patient out of hospital, and of giving him months or even years of useful

and active life which could never have been conferred by the older and conservative forms of treatment.

It is an unfortunate but undeniable fact that there still persists among some medical men even to-day a tendency to therapeutic nihilism, which even the brilliant discoveries of men like Sakel, Meduna, and others have not yet been able to dissipate. The author has heard this attitude concisely expressed in the saying " The schizophrenic is born, not made "—surely one of the most vicious half-truths ever propounded, and half-truths are nowhere more dangerous than when applied to medicine. This is certainly not the spirit which is needed for the attack on a major medical and sociological problem of this kind. It is regrettable that it is not always the lay public only whose mental attitude towards these disorders is in need of reorientation and reeducation.

What is required is a greatly extended and improved social psychiatric health-service provided with up-to-date centres equipped for the detection and early treatment of large numbers of psychiatric patients of all types. There should be a more thorough liaison between the psychiatrists and the general practitioners, who should be given every facility and encouragement to visit the psychiatric clinics, to follow up their patients, and to see the work for themselves. The general practitioner and medical student should receive special training in the early detection and handling of incipient mental disease.

It is becoming increasingly evident that the whole subject of cerebral biochemistry and its disorders is an enormous one, and that as our knowledge of it is added to and the present techniques of biochemical therapy improved and refined, this particular branch of psychiatry will become a highly specialized science in itself, in the same way as, for example, intracranial surgery or industrial medicine. The advent of the even more novel and promising operation of leucotomy seems likely to open up yet more new possibilities of approach to the therapeutic aspect of the problem. The immediate requirement at present is for a large number of keen and experienced psychiatrists who have had special training in these forms of treatment.

Our knowledge of cerebral physiology, the pathology of the metabolic disorders, and the mechanism of neurometabolic therapy is as yet only in its infancy, and the immediate future holds out limitless hopes and possibilities for research along these lines. It is not too much to hope that in the near future a co-ordinated attack by the biochemist, psychiatrist and general

physician will finally help to elucidate a problem which, up to the last few years, has always been one of the great unsolved mysteries of scientific medicine.

FINIS.

SCHEME OF CLASSIFICATION OF THE METABOLIC ENCEPHALOPATHIES

DYSOXIAS

Pure forms; symptoms entirely of dysoxic type, due to disorder of oxidation - mechanisms, respond only to anoxic therapy.

I. PRIMARY or ENDOGENOUS TYPE.

1. Malignant { simple / katatonic
2. Benign (manic-depressive)
3. Paranoid (sensory)
4. Derealization Type
5. Obsessional Type
6. Atypical

II. SECONDARY or EXOGENOUS TYPE.

1. Due to exogenous poisons—e.g., drugs, chemical poisons, toxins of infections.
2. Due to endogenous poisons—e.g. endocrine disorders, uræmia, diabetes mellitus.
3. Traumatic—due to brain-injury.
4. Due to external stresses—e.g., heat-exhaustion, battle-stress, climatic exposure, etc.

DYSGLYCIAS

Pure forms; symptoms entirely of dysglycic type, due to disorder of glycolytic mechanisms, respond only to hypoglycæmic therapy.

I. PRIMARY or ENDOGENOUS TYPE.

1. Malignant (hebephrenic)
2. Simple (manic)
3. Paranoid { Non-systematized (Paraphrenia) / Systematized (Paranoia)
4. Atypical

II. SECONDARY or EXOGENOUS TYPE.

1. Due to exogenous poisons—e.g., drugs, chemical poisons, toxins of infections.
2. Due to endogenous poisons—e.g. endocrine disorders, uræmia, diabetes mellitus.
3. Traumatic—due to brain-injury.
4. Due to external stresses—e.g., heat-exhaustion, battle-stress, climatic exposure, etc.

MIXED FORMS.

Contain admixture of dysoxic and dysglycic features, or alternating phases of dysoxia and dysglycia, due to disorder of both oxidative and glycolytic mechanisms, respond to combined anoxic-hypoglycæmic therapy. May be either of endogenous or exogenous form.

1. Combined Type—some forms of hebephrenia and katatonia.
2. Alternating Type—manic-depressive, some forms of hebephrenia and katatonia.

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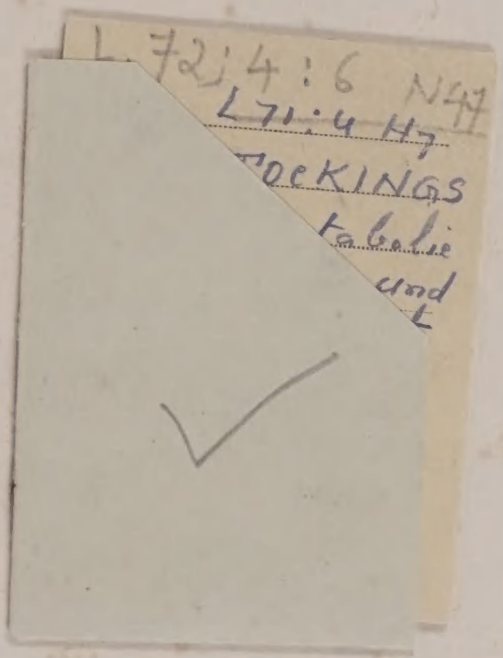
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